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The attached paper by Dr. Philip E. Enterline was presented at the 1983 Annual Hatch Symposium in Pittsburgh. This represents a very good discussion of the problems of distinguishing "natural clusters" of a disease in occupational population groups from clusters caused by health hazards in the workplace. This article is of great value in placing the results of our mortality surveillance program in proper perspective, and indicates some examples that we might use to explain the problem to our workers and to the public. Although Phil acknowledges the difficulties in explaining the problem to the general "lay" public, he does not offer any advice! It is of interest that he uses the Texas City brain cancer study to illustrate the difficulties with investigations of "clusters".

I believe that all corporate and divisional health and safety managers would benefit greatly from reading this paper thoroughly.

S. G. Austin, Sc.D.

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REACTING TO CANCER CLUSTERS IN THE WORKPLACE

by

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Clusters of Cancer

Our past experience and successes in detecting occupationally caused cancer and in identifying carcinogens in the occupational environment have made us alert to the potential of quantitative epidemiology for identifying new environmental hazards. Almost every week our attention is focused on an unusual disease cluster somewhere -- perhaps related to some hazardous human exposure. There must be literally hundreds of thousands of amature epidemiologists ready to alert health authorities to unusual disease experiences in the population. This is both a blessing and a curse. On the one hand, our past experience has shown that health surveillance is an important way to discover environmental causes of disease and insure continued progress in public health. On the other, intense surveillance clearly leads to many false alarms. Moreover, intense surveillance does not always lead to identification of a causal agent and may place government, industry, and labor in a difficult moral and ethical position.

Chance, of course, can play a role in the way disease occurs in a population. To understand this it is important to see what is meant by random. Table 1 shows three series of the numbers, 1 and 2. In the first row the 1's and 2's were placed in random order using a table of random numbers. In the second row, 1's and 2's were alternated, while in the third row they were clustered. If we were to observe number sequences represented by the

second or third rows in any population of numbers, we would suspect that some factor other than chance is at work and in the case of Table 1 this is true.

Of course, clustering and separation can occur by chance, so we can't be absolutely sure when we see a cluster that chance is not at work. Suppose we were to search for clustering in a series of events known by the way they were generated to be random. Table 2 shows a section drawn at random from a table representing a million random digits developed by the Rand Corporation many years ago.[1] There seems to be no clustering or separation of numbers here. Numbers appear to be in truly random order. Table 3 shows a section in the table of random digits we found by a little searching. Note here a cluster of 6 sevens in the center of the table. Clearly if we search random events we can find clusters of events that when examined in isolation do not appear random. Indeed, were we to test these selected observations for statistical significance they would probably be statistically significantly clustered. If we didn't know how they were selected, we could be misled into believing we'd discovered something.

Several years ago I was contacted by the Medical Director of the Shell Oil Company, and asked if I would be interested in conducting a study of workers who were using solvents -- benzene, toluene and methylethylketone -- to remove wax from crude oils for the purpose of making lubricating oils. The unit in which these men worked is appropriately called the lubes-dewaxing unit and the process they were using is common to almost the entire petroleum refining industry. I've been interested in solvents and their relationship to leukemia and felt here was a population that if studied might answer something about this relationship. Moreover, this study seemed to be moving from cause to effect rather than effect to cause. The effect to cause sequence is, of course, what happens when we discover a cluster and then search for the

reason.

Much to my surprise, my study showed an excess in prostatic cancer deaths.[2] I know of no reason why solvent exposure would produce cancer of the prostate. I might have expected an excess in leukemia, but found none. My report led to two other investigations of lubes-dewaxing workers in other refineries both testing a prostatic cancer hypothesis. One showed a small excess and one a small deficit.[3,4] The authors of the negative study thought perhaps my findings were due to chance, while the authors of the positive study supported their small excess with the findings from my study.

Last year it occurred to me to ask the Medical Director at Shell why he had asked me to do the study in the first place. I learned that the reason for the study was that workers at the lubes-dewaxing unit had noticed that several co-workers had died of prostatic cancer and wondered if it might have something to do with their job exposures. That is, they had detected a cluster. They reported this to plant management, plant management to headquarters, and I was asked to do a study. Of course, I could do nothing less than discover the prostatic cancers that were the reason for my doing the study in the first place.

Let's see what could have happened here. Suppose there are no exposures in the lubes-dewaxing unit that cause prostatic cancer but that there are many dewaxing units and some of these are being watched for disease excesses by workers, or management, or somebody's epidemiologist, or unions, or government in just the same way we searched tables of random numbers to detect a cluster. Under such scrutiny most watchers will discover nothing, but some are sure to discover something. Without knowing how many lubes-dewaxing units are being watched there is no way to evaluate the clusters discovered. It appeared from my study that exposures in lube-dewaxing units caused something,

when in fact I probably had no evidence one way or the other.

This is called the multiple comparisons problem in the statistical literature and it must be a very common problem in all scientific data gathering. When a series of data are examined and only parts are reported based on outcome, the common tests of statistical significance do not apply. It is possible, of course, to ask if a relationships is biologically plausible, but sometimes when dealing with cancer our data base here is limited.

To further illustrate how chance can create relationships, we had our computer generate 12 samples each consisting of 10 two digit random numbers. We then computed the 12 means shown in Table 4. Note that these means range from 34.8 to 62.4. We then tested the null hypothesis that the largest mean is not statistically significantly larger than the smallest and were able to reject this with a t test at $P < .05$. This is analogous to, for example, testing differences in IQ's of children born in various months of the year.

Giyen the manner in which the numbers were generated for Table 3, clearly the only reason for the difference is chance, and the reason for the significant t test is the way means were selected for testing. We violated the prime conditions set up for applying the t test in two ways. First, we examined all 12 means (in a series of 12) and selected only the extremes for testing, thus violating a condition of independence. Then we tested only the hypothesis that the larger number was significantly larger than the smaller number -- not merely that it was different. I had no <u>a priori</u> reason for doing this.

All this seems fairly obvious when we can see the big picture; that is, when we know everything that has been examined to yield our observations. It is not so obvious when we are shown only a piece of the big picture.

Unfortunately, there is often no way of reconstructing the big picture. Generally we know little or nothing about the conditions that lead to the selection of epidemiologic observations reported in the literature. We could call on our knowledge of biology, other epidemiologic observations, or just some good epidemiologic logic to convince ourselves that what is reported is not just a chance observation. Better still, we could develop a hypothesis and set about testing it with an entirely new data set. Usually verification takes time, however, and there is the moral dilemma in delaying action on findings when they may in fact be important. Even when we know how data are selected and how many comparisons have been made, how can a disease excess be dealt with when chance is a likely explanation?

Clusters within Clusters

Sometime ago the health manager for a paint manufacturing company called me about an excess in colo-rectal cancer observed in their workers. The company had participated in a national study involving 32 paint plants and they were one of three plants that showed an excess for this cause of death.[5] The excess was statistically significant ($P < .05$). My immediate reaction was that in 32 trys at least one and possibly two plants would have a statistically significant excess or deficit for colo-rectal cancer at the .05 level, and that this might have been only a chance occurrence. After all, $P = .05$ simply means that the null point hypothesis will be rejected incorrectly at this level one time in 20. In this case, a test of significance was in effect carried out not once but 32 times. Surely one or two of these should have been statistically significant by chance alone.

This was little comfort to the health manager. "What should I tell my workers?" he wanted to know. This did indeed pose a problem. I could hardly say that they didn't hve an excess, since the cases existed to prove that they

did. It would be difficult to explain that his plant was just unlucky. Clearly a situation like this calls for some further investigation.

There were twelve deaths from colo-rectal cancer in the paint plant cohort during the 12 year period 1958-70. This was over three times as many as would have been expected. Table 5 shows some data regarding these 12 deaths. Note the cluster of cases who were hired in the period 1950-52. This suggests that either there was a large build-up in personnel during the years 1950-52, or that there was some unique exposure for workers hired during these years that caused colo-rectal cancer, or that something else is going on. There was no personnel build-up in 1950-52. In fact, the largest hire year was 1946 with a fairly constant pattern of hires thereafter. Age patterns for hires also didn't differ much from year to year. How, then, could it be that seven out of twelve men who died of colo-rectal cancer were hired during the brief period 1950-52?

There are several interesting things about these seven cases. First note their ages at hire. The youngest was 39, and the oldest was 74 years of age. Second, all died of colo-rectal cancer in less than 19 years of date of hire (6-18 years). For most cancers we know that the latent period is usually much longer than this.

Obviously, the next move was to find out just what these seven men did in the paint plant and what their exposures were. There did not appear to be any common exposure at the paint plant that related these seven men to each other. The cases clustered but exposures did not. Moreover, I know of no substance or exposure to paint production that is related to colo-rectal cancer.

An obvious area for further inquiry was to see where the seven men hired during the years 1950-52 and who died of colo-rectal cancer worked before

coming to the paint plant. Recall that they were all 39 years of age or older at the time they were hired and must have worked for a considerable period elsewhere. The notations about previous employment on the personnel records did not suggest any comon earlier employment, but were too brief to be of real help. The paint company itself seemed to be "not guilty" and since it is in the business of making paint, and not cancer research probably shouldn't finance further inquiry. Moreover, the problem was too isolated to be of much interest to anyone else.

Can we really be sure that this cluster of cases was only a chance occurrence? Perhaps there was a causal factor involved. It's even possible that some new knowledge about the etiology of colo-rectal cancer lies buried here. My guess, however, is that this was indeed a chance cluster within a chance cluster and that further study would tell us nothing. I don't, know, however, how this kind of situation can be explained to the workers at the paint plant.

Starting with a Difference

After deciding what to tell the workers, it would be wise to see if any additional cases occur. One problem we would encounter here is whether to include in the study the cases that led to the study in the first place.

I recall something I read many years ago I believe was written by Donald Mainland about this problem, but in a context somewhat different than the one I've presented here. I've lost the reference but haven't forgotten the message. The setting was an NIH Study Section meeting called for the purpose of reviewing requests for additional support by investigators conducting clinical trials but who have run out of money. It does not seem unreasonable that some member of the Study Section would ask for a report on how each trial has gone up to that point before making a decision on continued funding. We

might call this an "interim report".

For one group of investigators things may be going all wrong. Perhaps the control group is actually doing better than the study group, or things are about even. A second group of investigators may report enthusiastically that things are going great. The treatment group is doing very well and with only a few more cases the difference between the treatment and controls will be statistically significant. Somehow the second group of investigators seems to be more deserving of support than the first and in the absence of other considerations some Study Section members may argue that they are clearly the most deserving of additional funding.

Not so clear, however, is the fact that if these members prevail a selection will have been made on the results to date, with the negative experiments likely to be terminated, and the positive experiments allowed to move ahead. Of course, those allowed to go on will include in their final report results to date. Such encouraging results are unlikely to be discarded. What in effect has happened, however, is that a new group of experiments has been initiated but this time the starting point is not the same for cases and controls, but rather somehow the starting point is one in which cases are given a head start. It's like a race between two runners in a 100 yard dash who are hypothesized to have equal running ability, except that one is given a 10 yard lead over the other. Who is likely to win?

This can be called the "interim report fallacy". It must be fairly common. Suppose instead of a NIH Study Section the sponsor is a drug company looking for a new product. Certainly it would be tempting to continue to invest in projects where a discovery is likely to be made and terminate the rest as early as possible. This example serves to illustrate a basic principal and that is, if you start with a difference you're likely to end

with a difference. So clearly the index cases that lead to an epidemiologic investigation and which generate a hypothesis can't be used to test that hypothesis. Some new independent observations are needed.

In actual practice is it really possible to ignore the index cases? Had I known that a cluster of prostatic cancer cases were the reason for my study of the lubes-dewaxing unit workers at the oil company, would I have been criticized if I left these cases out of my study? This is a tough decision to make.

To date I know of no one who has had the nerve to leave out index cases. A good example is the recent concern about brain tumors in the chemical industry. In 1978 an employee at a Union Carbide plant at Texas City, Texas, reported to the Occupational Safety and Health Administration that there appeared to be an unusual cluster of brain tumors among his coworkers. This stimulated an investigation by the company and an investigation by the government, both of which included the index cases.[6,7] Of course, both of the analyses of data from this particular plant showed an excess in brain tumors. How could it have been otherwise? On the other hand, neither the company nor the government could find any chemical exposure or exposures that were uniquely associated with these brain tumor cases.[8,9]

Employees have been notified by the company of the excess, but since the cause is unknown there appears to be nothing that can be done about it. This is a difficult situation for everyone. There are lots of questions. Should materials, manufacturing processes, or products be changed? Should brain tumor cases now be compensated by Union Carbide? Can or should anyone using products from the plant sue for third party liability?

CONCLUSION

As I read the history of occupational medicine my impression is that

nearly all of the important early discoveries proceeded from effect to cause, rather than cause to effect. Clearly we are still doing this so the situation isn't much different today than it was then. The difference is that because we're very sensitive to occupational hazards, and because we know that where they exist they can usually be corrected and lives saved, we are looking much harder and communicating much more effectively. All this has produced a great amount of information that is difficult to interpret and act upon.

I don't know why there was an excess in prostatic cancer among workers at a lubes-dewaxing unit in an oil refinery. I don't know why a cluster of colorectal cancer deaths appeared among workers in a paint plant. I don't know why a cluster of brain tumors appeared in a Union Carbide chemical plant. I suspect, however, that these observations could be analogous to the discovery of a cluster of sevens in a table of random numbers, and that we'd better think of some way to explain this to a public rapidly being conditioned to the notion that every effect has a cause, and the idea that failure to identify the cause is a failure in an elaborate mechanism now in place to safeguard the health of the American worker.

Table 1

Three Series of Numbers, One in Random Order

Group 1	2	1	1	2	1	1	2	1	2	2
Group 2	1	2	1	2	1	2	1	2	1	2
Group 3	1	1	1	1	1	2	2	2	2	2

Table 2

A Section of a Million Random Digits

36513	48937	41340
38382	65024	31159
93091	74743	40277
13302	15360	12996
06498	91705	39255
54267	82075	08290
45044	18070	02775
52814	95337	49272
87696	85560	69031
83262	38949	63965
06306	59335	84686
06179	28693	71801
93551	87645	99192
78082	13207	08320
05231	57430	21409

Source: p. 167, lines 8310-8324, Reference 7.

Table 3

A Section of a Million Random Digits Showing Clustering

44332	35906	00429
85439	92265	25291
84935	29656	50007
10792	88210	29374
48414	91067	68253
20349	71480	56852
46473	04122	57713
34304	77441	12104
22707	77770	31176
72877	41561	36903
77278	04880	23484
32936	00241	24803
36115	46717	15238
04858	67536	37041
09716	77255	65136

Source: p. 19, lines 905-919, Reference 7.

Table 4

Sample Means of Twelve Random Samples of Two Digit Numbers

Sample Number	Mean
1	47.3
2	41.3
3	62.4
4	34.8
5	55.2
6	48.8
7	48.0
8	49.5
9	42.2
10	60.3
11	57.7
12	49.0

Table 5

Twelve Cases of Colo-Rectal Cancer Occurring in a Paint Plant

Date of Hire	Age at Hire	Duration of Employment	Latent Period
1907	25	41	53
1921	28	42	52
1932	23	35	35
1943	56	8	33
1946	19	1	19
1950	52	16	16
1951	47	8	17
1951	74	6	14
1951	56	18	7
1952	39	18	18
1952	42	3	12
1952	63	3	6

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