

ASSESSING 4 CAUSATION

In this final chapter we will look at how epidemiologists attempt to establish causation, that is, to decide whether factor A can possibly be the cause of disorder or state B. Perhaps the earliest rules for assessing causation were Koch's Postulates, which were set forth about a century ago for determining whether an infectious agent is the cause of a disease:

1. Every diseased person (or animal) must have the organism;
2. It must be possible to isolate the organism and grow it in a pure culture;
3. A susceptible host, when inoculated with the organism, must develop the disease; and
4. The organism must be recoverable from the newly infected host.

While these could easily be applied to acute infectious diseases, there are many situations in which the rules do not apply. Sir Bradford Hill proposed a variation of these criteria that covers a greater variety of situations, which has been used with little modification ever since. These nine criteria, listed in descending order of importance, are:

1. The **strength** of the association;
2. The **consistency** of the association;
3. Its **specificity**;
4. The **temporal** relationship;
5. The **biologic** gradient;
6. Biologic **plausibility**;
7. **Coherence**;
8. Evidence from **experimentation**; and
9. **Analogy**.

We will use these criteria to examine one theory of the etiology of multiple sclerosis (MS). Multiple sclerosis is in many ways an intriguing disease. One of the most puzzling aspects is its geographic distribution; the prevalence seems to be directly proportional to distance from the equator. The disorder is far more common in the northern parts of North America and the southern parts of Australia and New Zealand than it is in the tropics. However, just to make things a bit more interesting, MS is quite rare in Japan, a country at the same latitude as California.

A number of etiologic theories have been proposed that try to account for this distribution of MS. These have ranged from a genetic predisposition to the disorder, to dietary factors, to exposure, and to canine excrement. One group of theories holds that MS is caused by a viral agent, possibly even a

slow virus (a class of viruses frequently invoked by researchers whenever the relationship between exposure and outcome is not readily apparent). In this chapter we will focus on one viral theory, exposure to the measles virus, to see whether it is a plausible explanation.

THE CRITERIA

STRENGTH OF ASSOCIATION

This criterion holds that the stronger the association between the supposed cause and the effect, the greater the chances are that a causal relationship exists. In this example there should be a higher rate of multiple sclerosis among people who have been exposed to the measles virus than among those who have not been exposed. Conversely, measles antibody titers may be higher in MS patients than in people who do not have the disease.

The data in this regard are tantalizing, but unfortunately they are also inconclusive (this can cynically be called the "So what else is new?" effect in epidemiology). Adams and Imagawa found that various measles antibody titers were higher in MS patients than in normals. However, as can be seen in Table 4-1, the magnitude of the difference is not overly large in this study or in later ones, although a trend is definitely present. Thus, on the basis of this criterion, the case for causality is not ruled out, but does seem somewhat weak.

CONSISTENCY OF ASSOCIATION

The association between the suspected cause and the outcome should be seen across numerous studies, ideally by different research teams, in different settings, and under different circumstances. The larger the number of studies that demonstrate such a relationship, the stronger the evidence. There have been about 35 such studies conducted since 1962, and higher titers of measles antibodies were found in MS patients in all but four of them. So this criterion would lend support to a causal hypothesis involving exposure to measles.

TABLE 4-1 Percent of Subjects Over or Under 32 on the Serum Dilution Test for Measles Virus

	MS Patients	Controls
< 32	64	86
> 32	36	14

Reciprocal of
Serum Dilution

However, in and of itself consistency does not *prove* association, much less causation. (Indeed, none of the criteria proves causation; they can only be used either to strengthen or to weaken the case for it.) All of the studies can suffer from the same types of bias, or the association can be in the opposite direction. For example, a number of studies showed that the use of conjugated estrogens was associated with a much higher risk of endometrial carcinoma. However, Horwitz and Feinstein pointed out that all of the studies suffered from the same type of sampling bias: women were identified on the basis of vaginal bleeding. Estrogens may cause bleeding, which leads to an intensive work-up during which the cancer is discovered. It is possible (indeed, they found it probable) that endometrial cancer is almost as prevalent in the general population, but women who did not take estrogens didn't have the symptom of vaginal bleeding, and so their cancer was not detected (see the discussion on subject selection biases in *Threats to Validity*). When the bias was eliminated, the odds ratio dropped from 11.98 to 1.7, or in essence from a twelvefold risk of developing cancer for women who have used estrogens to less than a twofold risk.

SPECIFICITY OF ASSOCIATION

Ideally, the cause should lead to only one outcome, and that outcome should result from that single cause (Fig. 4-1). Unfortunately, life is rarely this simple. Obviously not everyone who gets measles later develops MS; measles can lead to a host of other adverse outcomes (including sterility), and it is quite possible that MS is multidetermined and has other causes (e.g., genetic predisposition, exposure to other viruses). To use another example, obesity increases the risk not only for stroke, but also for diabetes; however, both diabetes and stroke can arise from causes other than obesity.

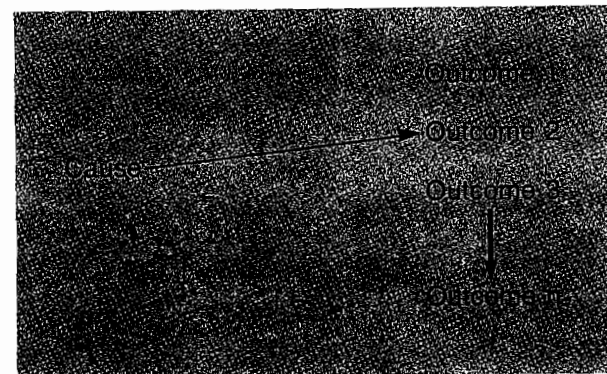


Figure 4-1 Ideal specificity of association.

When specificity does exist it can be a very powerful argument for causality. For example, the annual rate of malignant mesothelioma is extremely low, averaging fewer than three cases per million for males and about 1.4 cases per million for females. The incidence of mesothelioma among asbestos workers, however, is 100 to 200 times higher. It has also been estimated that there was exposure to asbestos in at least 85 percent of the mesothelioma cases; indeed, even this very high figure may be an underestimate, since families of asbestos workers are at risk through fibers brought home on clothing. It would seem from this evidence that there is a high degree of specificity, because exposure to asbestos is found in nearly all cases of mesothelioma.

Thus, if there is specificity of association, it strengthens the case for causality. However, a lack of specificity does not necessarily weaken the case.

TEMPORALITY OF ASSOCIATION

For factor A to cause outcome B, A must precede B (Fig. 4-2). That is, the person must have been exposed to the putative cause before the onset of the disorder. While this may appear so self-evident that it hardly bears mentioning, it is indeed difficult to establish in many cases, especially for chronic conditions with long latency periods. In the case of MS and measles it is obvious that the *clinical onset* of measles precedes that of MS; however, it would have to be shown that MS did not have a long, insidious onset that may have begun *before* the person contracted measles.

To use a different example, a number of studies demonstrated that a low serum cholesterol level was associated with a higher risk of cancer, which led some to postulate that a low cholesterol level somehow results in cancer. Recently, however, Dyer showed that the more likely explanation is that undetected cancer leads to a lowering of the cholesterol level. Thus, the purported "cause," cholesterol level, may actually occur *after* what was supposed to be the "effect," cancer.

One field particularly prone to problems in interpreting temporality is psychiatry, especially with respect to those studies that try to uncover family patterns that predispose people to major disorders. Since many problems manifest themselves only when the patient is in his/her 20s or 30s, the vast



Figure 4-2 Temporality of association.

majority of studies use either retrospective case-series or case-control designs. The assumption made is that any family dynamics uncovered were present prior to the onset of the disorder. For example, the supposed etiology of early infantile autism was once thought to be the emotional coldness and withdrawal of the parents, and especially of the mother. However, later studies indicated that these attributes were more likely the parents' reactions to an unresponsive infant, rather than the cause, thereby supporting what parents have long maintained: insanity is inherited — we get it from our children.

BIOLOGIC GRADIENT

The biologic gradient, or dose-response relationship, states that if more exposure leads to more of the disease, the case for causality is strengthened. This would imply that those who had more severe cases of measles should be more likely to develop MS, or to develop more serious symptoms earlier on. The evidence in this regard, however, is lacking. The biologic gradient is seen most clearly with regard to toxins and carcinogens. Newhouse, for instance, cited data gathered by Merewether and Prince that showed the relationship between length of employment in the asbestos industry and the incidence of fibrosis. The data look something like Figure 4-3. There seems to be a definite trend, in that longer exposure to asbestos results in a greater proportion of people who develop fibrosis.

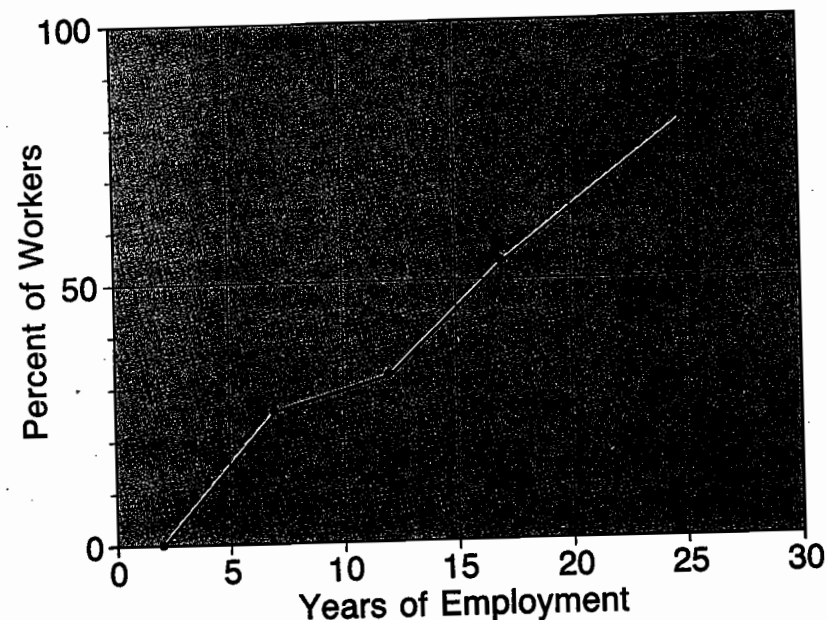


Figure 4-3 Length of employment in asbestos industry versus incidence of fibrosis.

For less obvious causal relationships there may be an amount of a toxic agent below which there are no adverse effects (at least none that we can measure with our current technology), and a ceiling, whereby no further increase leads to a greater effect. Some people postulate this is the case with ionizing radiation; there is no increased risk for cancer if exposure is below a certain threshold, whereas death is a certainty above an upper limit. Between these upper and lower limits, however, there may be a dose-response relationship.

BIOLOGIC PLAUSIBILITY

If the association makes sense from the perspective of biology, there is a (somewhat) greater plausibility, if not probability, of a causal relationship. Thus, although the etiology of MS is still unknown, there is evidence from related disorders that viral infections, and especially measles, can result in demyelination in the central nervous system. For example, high measles antibody titers are found in the serum and cerebrospinal fluid of patients with subacute sclerosing panencephalitis. This would indicate that a causal relationship between measles and MS is at least within the bounds of possibility.

However, a lack of plausibility may simply reflect our incomplete knowledge of physiology and biology. Until recently no known mechanism existed to explain how psychological stress could result in a greater susceptibility to infectious diseases and cancer. Only within the past few years has it been shown that stress may produce immune suppression by affecting immune cell function. As was the case with the criterion of specificity, plausibility strengthens the hypothesis, but a lack of plausibility does not weaken it.

COHERENCE

When discussing biologic plausibility, we noted that the absence of a plausible explanation was not necessarily damning to a good theory; it may simply reflect our ignorance. By the same token, the postulated causal relationship should not conflict with what is generally known about the disease or disorder.

For example, we mentioned that the prevalence of MS seemed to be proportional to the latitude, with some exceptions in Asia. However, the geographic distribution of measles is, if anything, opposite to what one would want; it is more common in the tropics than in more temperate climates. Using the criterion of coherence, this would argue against a causal link between the two diseases.

Needless to say, theories have been proposed to explain this inverse relationship. It has been postulated that subacute cases are common below the age of 15 years in the tropics, and that this early infection provides protection against later, more serious ones. This may be taken as an example of Edington's Theory: "The number of different hypotheses erected to explain a given biologic phenomenon is inversely proportional to the available knowledge."

EXPERIMENTAL EVIDENCE

In some cases there may be experimental evidence that can show a causal relationship. This evidence can be of many types: "true" experiments in the lab, randomized trials, animal models, experiments in nature, or interventions in which some preventative action is taken.

An experiment in nature would exist if a place were found where MS had been nonexistent until the society was introduced to the many benefits of civilization, including measles. This may indeed have been the case in the Faroe Islands. MS suddenly appeared in 1943, with 24 of 25 of the known cases first appearing between then and 1960, which is consistent with a mean age of onset of about 25 years. This "epidemic" coincided with the invasion of Denmark by Germany in 1940, and the subsequent stationing of about 800 British troops on the islands 4 days later. Although not conclusive evidence in its own right, this naturalistic experiment strengthens the case for MS being caused by some form of infectious agent.

Since an effective vaccine for measles was introduced to North America in 1963, there has been a dramatic decline in the prevalence of subacute sclerosing panencephalitis. If there is a causal relationship between measles and MS, we should begin to see a similar drop in MS starting about 25 to 30 years later, or some time around 1990. This would be an example of experimental evidence from an intervention. In this case, as in many others, the treatment was not predicated on an assumed relationship between the cause and effect; the aim of vaccination was simply to eliminate measles, not MS. Any evidence of a reduction in the incidence of MS would be a side benefit, probably unanticipated at the time the vaccination program began.

Experimental evidence again strengthens (but does not necessarily prove) causation. However, as with most of these criteria, its absence does not weaken the case because it is often extremely difficult or unethical to do the types of studies that would yield less equivocal results.

ANALOGY

The weakest form of evidence regarding causality is arguing from an analogy. Returning again to the example of measles and subacute sclerosing panencephalitis, we can state that just as measles can cause one form of demyelinating disorder, it is reasonable to expect that it can cause another.

In this regard analogy is very similar to biologic plausibility. For this reason, some authors don't distinguish between the two and drop this last category from the list of criteria for causality.

SUMMARY

Even if a theory passes all these criteria with flying colors, it does not necessarily prove causation beyond any shadow of a doubt. However, the more criteria that are met (especially the ones near the top of the list), the more likely it is that the causal hypothesis is in the right ball park, given the

current state of our knowledge. Newer discoveries, however, may cause us to modify or even discard our cause-effect theory, and to replace it with a different one. Buck notes that we would prefer a new hypothesis to a well-established one only if it meets at least one of the following criteria:

1. The new hypothesis makes more precise predictions than the old one;
2. More observations are explainable with the new hypothesis;
3. Previous observations are explained in more detail;
4. The new hypothesis has passed tests that the older hypothesis has failed;
5. It suggests tests or makes predictions not made by the older hypothesis; or
6. It has unified or connected phenomena not previously considered to be related.

Thus any causal hypothesis should be seen as just that, a hypothesis that accounts for what we know now, but that may be modified or overturned at any time.

C.R.A.P. DETECTORS

C.R.A.P. DETECTOR IV-1

Question Ney used the statistic that the "rate of increase in child abuse parallels the rate of increase in abortions" to argue against abortions. Although he didn't calculate it, the correlation between the number of abortions and the number of cases of alleged physical ill treatment in Ontario between 1971 and 1977 is 0.85. Does this high correlation support Ney's case for a causal association?

Answer One of the cardinal rules of statistics is that you can't draw causation from a correlation. In fact, we calculated that the correlation between the number of child abuse cases and the number of high school graduates during the same period is 0.86, and between cases of abuse and the gross revenue of Canadian railroads is 0.92. Nobody would argue, however, that the way to curb child abuse is to cut enrolment in high schools, or to make the railroads lose money.

A nice demonstration that strong correlation does not necessarily imply any meaningful relationship is shown in Figure 4-4, which plots the number of wins in 1984 by teams in the American Football Conference as a function of the number of letters in the team name. The correlation between these two variables is 0.70, a figure high enough to cause most researchers to have dreams of tenure.

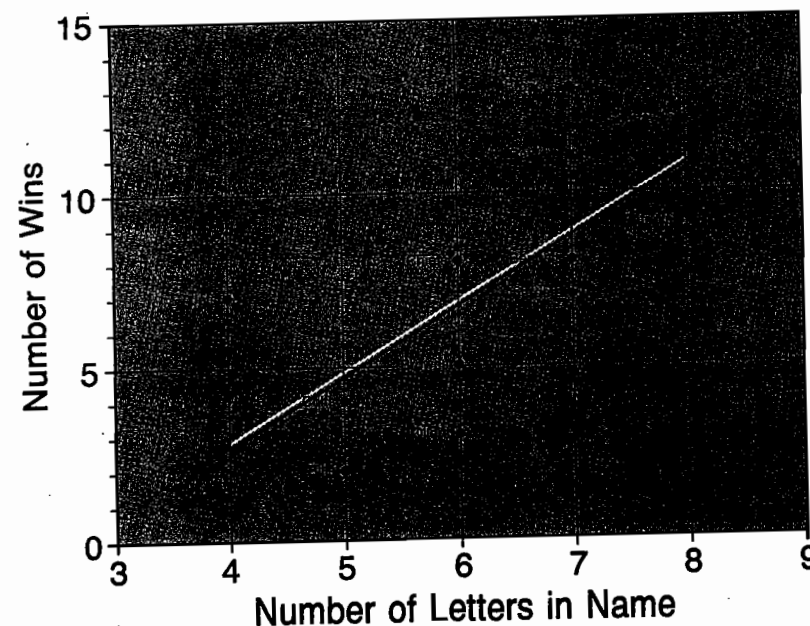


Figure 4-4 Relationship between wins by football teams and number of letters in their names.

C.R.A.P. DETECTOR IV-2

Question There has been concern expressed recently that the low rate of infection from measles has caused parents to become complacent and not have their children immunized. The fear is that there will be an outbreak of measles, with the attending death rate that used to characterize the infection. Is this a concern? Was the vaccine responsible for the marked reduction in the case fatality rate from measles?

Answer Not according to McKeown. Figure 4-5, based on the graph in his book, *The Modern Rise of Population*, shows that the decline in the mortality rate from measles among children began long before the immunization program was initiated. This reflects the importance of establishing a temporal relationship before anything can be said about a causal one.

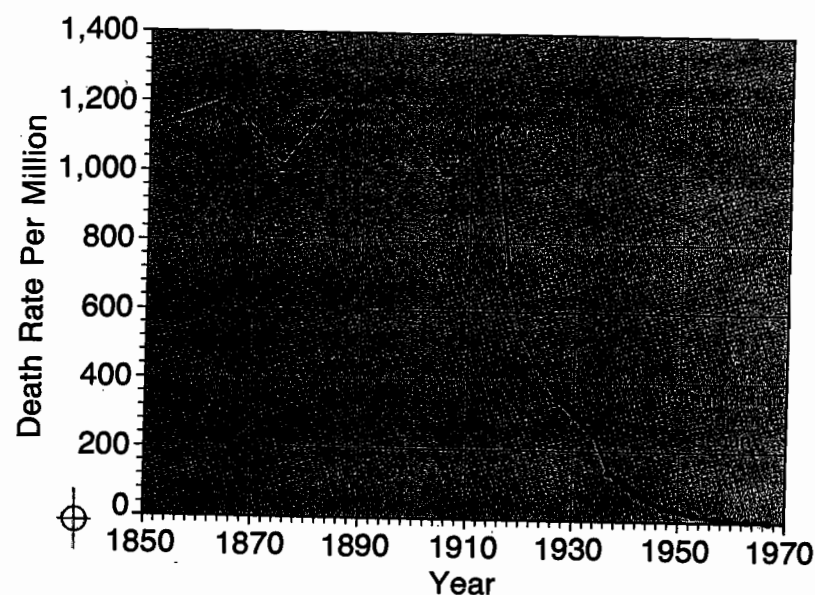


Figure 4-5 Mortality rate from measles over time. Data from McKeown T. *The modern rise of population*. London: Edward Arnold, 1976:96.

C.R.A.P. DETECTOR IV-3

Question A group of researchers in England found that bus drivers had a higher rate of coronary heart disease than did conductors. One hypothesis put forward to explain this was that conductors had to run up and down the stairs of the double-decker buses, whereas the drivers spent all day on their (and the buses') seats. Thus, it may be that a more sedentary job increases the risk of heart disease. Is this a viable explanation for their results?

Answer Only if all other differences between drivers and conductors are ruled out. The same research group compared the body builds of the two groups by doing an "epidemiologic survey" of their uniforms! As Figure 4-6 shows, a larger proportion of drivers than conductors had trouser waists of 36 inches or more, irrespective of age. So it would appear that there may have been constitutional differences between the groups from the very beginning, which makes an interpretation based on other group differences chancy at best.

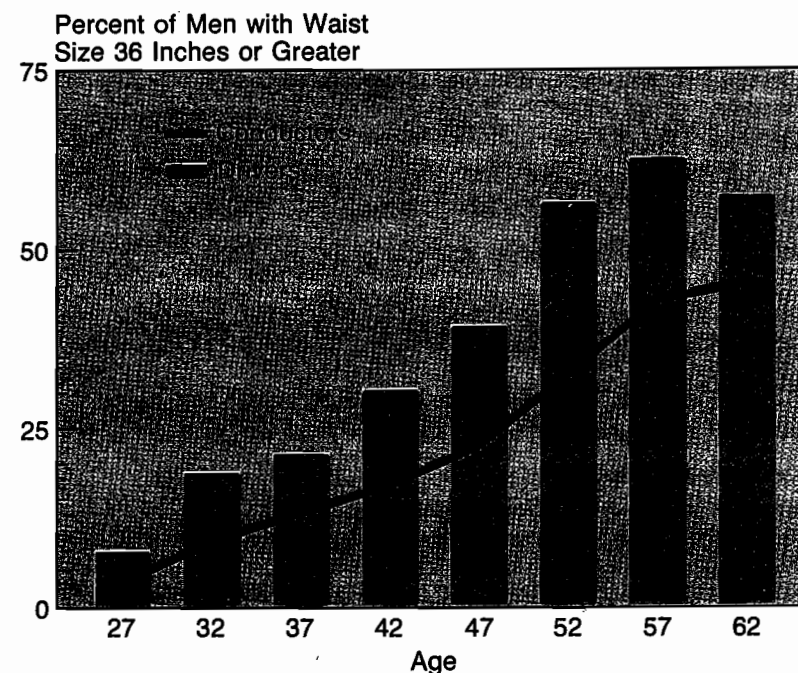


Figure 4-6 Waist size of conductors and drivers versus age.

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APPENDIX

A Brief Epidemish-English Dictionary

In the course of writing their reports and journal articles, researchers in epidemiology often use words or phrases whose meanings are somewhat obscure. To assist the reader in understanding these terms (and to provide a little amusement), we provide herewith a brief dictionary.

To begin, we offer the definition of clinical epidemiology (itself an obscure term), which is credited to Dr. Stephen Leader of the University of Sydney:

"Clinical epidemiology is that branch of alchemy whose goal it is to turn bulls-t into airline tickets."

And now to the dictionary:

*When The Researcher Says**He/She Really Means*

A trend was noted.

The statistical test was not significant.

The demographic characteristics of the nonresponders were similar to those of the rest of the sample.

All we really had on them was age and sex.

Agreement between the raters was acceptable.

The agreement was so bad that we don't dare to include the actual number in the paper.

The questionnaire was circulated to a panel of experts to establish face validity.

Our friends liked it...and the bottle of scotch we included.

The rate of lung cancer among the hourly rate employees was significantly higher, which may be caused by excess PBCP exposure.

It might also be caused by obvious things like smoking and social class, but I'm interested in PBCPs today.

In a case series of 12 patients nine showed clinically significant improvement on the experimental drug.

With the help of the drug company representative, I judged which patients got better under my care.

The correlation was highly significant ($p < 0.0001$).

With 10,000 subjects, *any* correlation is highly significant.

The response rate was 60 percent, which is acceptable for studies of this type.

Although there was no overall difference in mortality, the rate of left clavicular cancer was higher in blue-eyed females in the exposed group.

While the results appear to be consistent with the predictions, further research is warranted.

Further research is required to clarify the results.

The difference was statistically significant ($p < 0.0001$).

The study was a single-blind trial.

A retrospective study was conducted.

Morbidity and mortality from Blum-Streinorman's disease represents a significant burden on society.

The overall agreement was 87 percent, which represents a truly remarkable rate of agreement ($Kappa = 0.12$).

Based on current trends, the incidence of self-pollution in the year 2000 will be...

It is widely known that...

A one-tailed test was used.

However, the study itself was so bad that even a 100 percent response rate wouldn't have saved it.

If you look at enough things, sooner or later one of them is bound to turn out to be significantly different.

I've already applied for a new grant this year.

I haven't a clue what it all means.

...but clinically useless.

Everybody knew who was getting what except for the poor patient.

We had all these data sitting around, and needed some fast publications.

It's my own narrow interest, but I have to justify the research somehow.

Chance corrected agreement was so abysmal that we thought we had better talk about raw agreement.

Draw a straight line through the data from one hospital in 1970 and 1980 and that's what we got.

I can't be bothered to look up the reference.

The results wouldn't be significant with a two-tailed test.

After adjusting for baseline differences between the groups...

After adjusting for confounders...

One possible explanation for these results is...

Forty patients agreed to participate.

After conducting a pilot study, we decided to use a mailed questionnaire.

After conducting a pilot study, we decided to use face-to-face interviews.

The data were normalized by truncating outliers.

We did not include premorbid status and number of previous hospitalizations in the model.

The agreement between raters was
excellent
good
acceptable
low

Data was analyzed using the Schmedlap-Scheisskopf test.

We did a lousy job of randomizing.

Boy, did these groups differ!

I can only think of one.

The others were able to pay their hospital bills.

We got tired of people slamming the phone in our ear.

They wouldn't return the mailed questionnaires either.

We couldn't get the results we wanted, so we threw out subjects until we got what we were looking for.

We forgot to gather these data.

good
fair
nonexistent
negative

We tried the usual tests but they didn't give significant results.

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