Fraud in Medical Research

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In the fall of 1963 my four-year-old daughter Suzie, who has since graduated from MIT, predicted my future. A neighbor had inquired over the back fence "What does your daddy do?" Suzie replied, "He used to be a doctor but he doesn't work any more." We had moved to Bethesda from Boston a few months earlier, and my job had changed from Resident in Internal Medicine at Massachusetts General Hospital to Research Associate in the Laboratory of Biochemistry at the National Heart Institute. Since that time I have not "worked," rather I have enjoyed the great fortune of doing what I please—medical research. I feel very fortunate to have been allowed to pursue problems on my own terms and am extremely grateful for our system of support for medical investigation. It is therefore with regret that today I discuss a vexing problem, that of fraud in medical research. I am revolted by anyone who fabricates results in the laboratory. I cannot explain such an individual nor can I justify his actions in any way. However, in approaching the question of fraud in medical research, I will attempt to put my personal revulsion aside. It is easy to overreact and it concerns me that we in the medical research community may do just that, even though I can understand why. It is hard to be dispassionate about something that strikes at the heart of our lives. However, by overreacting we may invite the formation of regulatory groups that will impede, rather than facilitate honest medical research.

In the past few years, there have been a half-dozen scandals involving outright fabrication of research data. These episodes have received wide press coverage, both because of intrinsic prurient interest in such news and because cheating in the use of a method where the goal is the discovery of truth is so aberrant. It's like trying to construct a building using dynamite—it does not work.

Why does the scientist cheat? The number of episodes of dishonesty seems to be increasing. Several factors may account for this. First, the number of investigators involved in medical research as their major career effort has increased enormously. At the second annual meeting of the American Society of Hematology held in St. Louis in 1959, there were 41 submitted abstracts; in 1981 there were 875. The membership of the American Federation for Clinical Research has tripled since 1962, and since 1968 the number of investigators in clinical departments of medical schools has increased from 11,000 to 30,000.

Of possibly more significance is the fact that there is a qualitative difference between today's investigators and those of the past. The physician-investigator used to be just that—a physician first and an investigator second. The stake in "results" was less. One had medical practice to fall back on if things didn't work out in the laboratory. This allowed for a gentlemanly practice of science which, although competitive, did not produce the pressures of current times.

As biology has become more technically complex, it has become more and more difficult to be both a physician and an investigator working at the forefront of medical research. Thus, to most of us, medical practice as a fallback position has become an increasingly unrealistic alternative to an unsuccessful investigative career. The pressure to produce is inevitable and although this does not *cause* cheating, it may contribute to a loss of perspective. We have all had the experience of the spurious spectacular result that leads to temporary euphoria, only to have our hopes dashed when the controls were completed or the artifact discovered. How tempting it is not to look too hard for that "fly in the ointment."

A second reason for the increased recognition of cheating scandals has come because the public's per-

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ception of medical research has changed. When I entered the field, investigators were judged by the public as absentminded dreamers of little interest to men of affairs. If we did something of benefit to mankind, great! If not, no one really cared. Recent successes in clinical investigation and in molecular biology have convinced the public that biological research is useful and important. Thus, a new reward is potentially available to the investigator. He can become a "star" in the eyes of the public. No longer need he fumblingly describe what he does at family reunions to incredulous relatives, the epilogue being delivered by the patriarch: "Don't worry, he'll come to his senses and hang out his shingle soon."

The increased awareness in the activities of medical investigators means that our foibles are front page news and not just gossip for the laboratory coffeeklatch. I believe that striving for "stardom" is a perverse motivation for a scientist and it is a major factor in some cases of fraud. A number of other conditions contribute to the likelihood of dishonesty. These include the unscrupulous mentor who pressures fellows and students for "results" to obtain or maintain stardom, thereby suborning them, and the "absent" mentor who assembles large groups of students and fellows and sets them to work without adequate supervision, thereby failing to expose them to the skepticism and rigor important to the scientific method. A recent report on dishonesty in research by an *ad hoc* committee to the dean of the Harvard Medical School listed additional factors that could foster dishonesty, such as excessive publication of fragmentary results and multiple abstract submissions.

What is the significance of fraud to progress in medical research? Fraud affects medical research in two ways. The first is to sully the "white knight" image that the public has afforded investigators. There can be no doubt that recent scandals have tarnished our public image, albeit deservedly so. However, the public's increased interest in, and knowledge of, medical research means that they are beginning to know us better; thus, they will inevitably discover that we are no better or worse than other people. Therefore, I conclude that our loss of revered status, though regrettable, is inevitable. Not only is it inevitable, but, in fact, may be good. A public imbued with a healthy skepticism is a valuable ally.

The second, and potentially more important, way that fraud may affect medical research is to retard progress. Fabrication of research results has been of two types. In the first, the claimed results are of great significance to a fast-moving field, or of great theoretical or practical importance that would open up new areas for investigation. Thus far, in these instances where the damage would be potentially great, the false results have been refuted or the fraud discovered within a few months. In other cases, the work itself has been of little apparent significance being either primarily confirmatory or data-gathering that I categorize as "brownian motion research." That is, movement without progress. In such cases, one could argue that no one cares whether the work is right or wrong. Even the claim that money is wasted in refuting such frauds is discounted by my contention that investigators who are likely to make lasting contributions are unlikely to waste time on such projects.

In thinking of ways that fraud could hinder progress in medical research, I believe that the most damaging fraud might be in a field where the claims are significant, but the experiments are so complex as to take years to repeat. This is possible where the results of a particular therapy would take years to evaluate. Although at present I know of no such cases, their occurrence would be very serious. Probably the complexity of such experiments involving many investigators renders fraud unlikely. Dishonesty in such cases would require the conspiracy of many workers.

Fraud is a fabrication of results, either from "whole cloth" or by the techniques of "data management," such as, "buffing up the curves" or throwing out results that do not conform. However, a much more insidious danger faces the investigator than outright fraud, the problem of self-delusion. I mentioned earlier the spurious spectacular result that leads to temporary euphoria and the temptation not to look for the fly in the ointment. Human nature cannot be denied. We have all indulged in self-delusion at one time or another. However, it has no place in the laboratory. Self-delusion involves misinterpreting one's own results. This can follow from events as simple as omitting proper controls or failing to repeat complex experiments that conform to preconceptions. In fact, I believe that self-delusion occurs most frequently when an investigator anticipates the result of an experiment before it is performed. In this case, "aberrant" features of the results are either ignored or discarded as unimportant, when in fact they are the key to progress. I will give a hypothetical example to illustrate this point.

An experiment is designed to evaluate the effect of vitamin K on the in vitro synthesis of prothrombin by cultured liver cells. Cells are incubated with radioactive amino acids with and without vitamin K, and newly synthesized radioactive prothrombin is isolated by immunological techniques. Fig. 1 shows the results of four experiments with stimulation by vitamin K plotted vs. time. Note that in all four experiments a "positive result" is obtained. Also note that the synthesis of prothrombin with time is not really linear. In each experiment there is a "glitch" in the curve

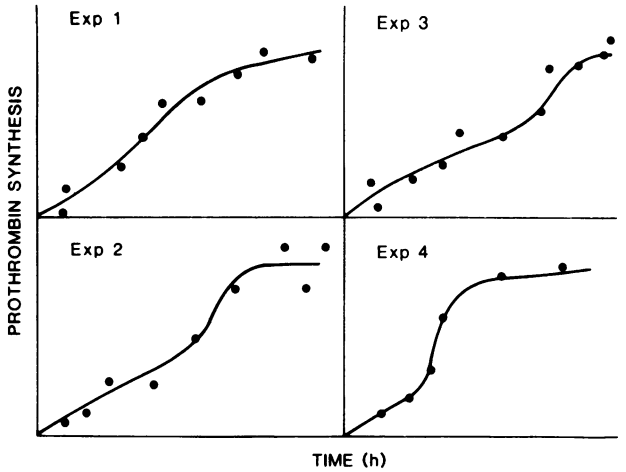

FIGURE 1

where it seems that prothrombin accumulates in a greater than linear manner at a variable time after institution of the culture. Our hypothetical investigator ignores this aberration and instead "normalizes" the data and averages the four experiments as shown in Fig. 2. A line is drawn through the points; the original hypothesis that vitamin K is required for prothrombin synthesis is validated. The work is then written up and a paper is submitted for publication. In the interests of "conserving space in the journal" the editors insist that only the summary graph be published. Thus, we have "lost" information to all but those evaluating the original data. Suppose another worker has the idea that degradation products of prothrombin that result from its proteolytic turnover serve to regulate prothrombin synthesis by stimulating its production. This hypothesis would predict that as prothrombin is synthesized and then degraded by the inevitable proteases present in tissue culture media that synthesis would accelerate. The second investigator might be dissuaded from pursuing the hypothesis upon examination of the published results of the first worker. Yet, in fact, the raw data of those experiments are consistent with the hypothesis. Thus, although no fraud has occurred, progress has been potentially retarded. In my five years as an editor of The Journal of Clinical Investigation I handled over 6,000 papers. I found dozens of examples of self-delusion and only two cases involving fraud.

What should be done to prevent dishonesty in science? The current wave of publicity about dishonesty in science has led the NIH, the American Association of Medical Colleges, and several institutions to form committees to study the matter. Questions addressed include: What can be done to prevent erosion of public confidence in the honesty of the biomedical research community? How can institutions promote ethical conduct in research? At what levels should measures be applied to prevent fraud—government? journals? institutions? individual laboratories?

In studying the recent cases I would argue that the current methods for dealing with dishonesty in science, although imperfect, have meted out stern punishment for wrongdoing. The guilty parties have been effectively excluded from further pursuit of careers in medical research, and even co-workers who may have been partially culpable to totally innocent have suffered irreparable damage to their reputations. I recommend that some additional policies should be adhered to in investigating cases of alleged dishonesty in science. These include: (*a*) retraction of all papers relating to the work in question, even if parts of those papers are not in dispute; (*b*) no further publication of any papers involving work of the accused until all issues have been resolved; (*c*) investigation of the details of the reported fraud by a group that does not include anyone from the involved laboratory or their close associates; and (*d*) suspension of any *new* grant awards to the accused until the issue is resolved. I do not want to discuss today how or by whom these policies should be applied. Rather, I will speak about methods for prevention of fraud. Can government work to prevent dishonesty?—Unlikely. The NIH bureauracy is too far removed from the daily activities of the laboratory. Furthermore, experience with NIH remedies shows that the treatment is often worse than the disease. A recent example involves the guidelines for recombinant DNA research. Although the impetus for the guidelines came from molecular biologists themselves, in practice the guidelines almost hamstrung the most promising new avenue of scientific research in decades.

In that case, the *real* issues were technical. What are the likely benefits to society of recombinant DNA research vs. the likely dangers of the new technology? In retrospect, it is easy to see that the benefits were obvious and concrete while the risks were entirely hypothetical. Yet the controversy was quickly changed

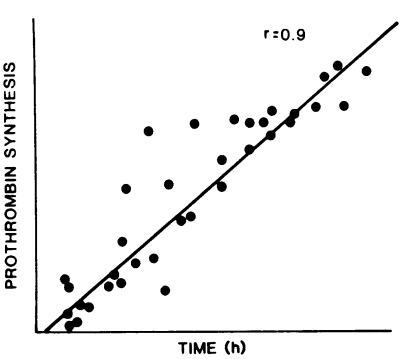

FIGURE 2

from the technical issues to moral and philosophical concerns. Various splinter groups sought to ban recombinant DNA research, not on the grounds of specific dangers but rather because of fears inspired by *Brave New World*. As James Watson said, "A tiny group of Boston-based academic leftists fantasize that the rich will finally subjugate the masses by giving them bad genes manufactured by recombinant DNA methodology."[1] Only through many hours of lobbying and education of politicians and administrators was it possible to continue the research and eventually to disarm the guidelines.

A lesson can be learned from this episode. A scientist who becomes inactive may lose his ability to judge technical issues. Since ex-scientists and other administrators could not validly judge the technical issues, they attempted to "solve" the DNA problem by guidelines. The guidelines were established and enforced by committees.

In my opinion, rigid rules or "guidelines" are often used as methods to avoid judging issues on their specific merits. This strategy is used by institutions wishing to avoid individual responsibility and by administrators who, as "supernumeraries" less capable than those they wish to control, use rigid rules to avoid confronting the substance of problems. Collective decisions mean that individuals are not directly accountable. We have all been frustrated by verdicts rendered by such groups as "the council" or "the editors." It reminds me of the firing squad where no one executed the victim because one gun had a blank. Therefore, I would argue that government has little to offer to the solution to the problem of prevention of dishonesty in research. The same arguments apply to a lesser degree to institutions, as a whole, such as universities or large research institutes.

Suggestions that journals take a greater role in ensuring against publication of false data are also impractical. We are the JCI not the FBI. The most that a journal can do if the reviewers or editors suspect that data are either false or, as is more often the case, wrong for less sinister reasons is to refuse to publish the work. Journals have no mechanism to investigate whether data are false or not. Even when fraud is discovered, journals are in a poor position to respond. In most cases of fraudulant papers, there are several authors. One or more is accused of cheating and the others are presumably innocent. Journals have no way of sorting out the guilty from the innocent. In my opinion when any part of a study is found to be fraudulant, the entire work should be retracted pending its repetition. This has not always happened in practice as authors have asked to retract only parts of the data in papers. In only one instance of a dispute between authors in my time with the JCI was I able to communicate with all of the authors of a disputed work, thereby sorting out the facts of the case. In that instance, fraud was not an issue. Let me illustrate the problem for journals by another hypothetical example. Suppose a paper with three authors is published in which a variety of types of measurements are made. Later, two of the authors write to the journal stating that the work of the third author is false and therefore should be retracted while the remainder of the work should stand. We hear nothing from the third author whose guilt or innocence has not been established. If the journal publishes a conditional retraction of the work, the third author is convicted of wrongdoing without any hearing. As recent scandals have illustrated, such a conviction will destroy the reputation of this worker. Thus, other mechanisms are required to prevent and punish fraud. The journals can play only a passive role in this regard.

What can be done to prevent publication of false work? I believe that the only level at which any effective measures can be applied is in the individual laboratory. Students, postdoctoral fellows, and junior colleagues are the future of medical research. They are our most valuable resource and should be treated as such. Senior investigators have a solemn responsibility to guide trainees to allow them to express their full potential. If, because of clinical, administrative, or other constraints, an investigator does not have the time to participate in the ongoing progress of an investigation on a *day-to-day basis*, then he should dissociate himself from it. It is another type of self-delusion for a senior investigator to claim "It was my idea" or "I wrote the paper" or "It's my grant" as justification for taking trainees into the laboratory but not directly participating in the work. The contribution of the senior investigator in such cases is miniscule. It's rather like claiming credit for writing *Hamlet* because you furnished Shakespeare with a pencil. In such laboratories the training environment may still be good if advanced trainees or technicians are outstanding, but that is uncommon in my experience. The worst aspect of this situation is that lack of supervision leads not to dishonesty but more often to lack of productivity and progress due to the investigation of trivial problems.

Work in progress should be discussed openly and the data should be reviewed frequently, not just by the laboratory chief but also by disinterested parties. Group meetings of large laboratories where there is evaluation of data of individuals are important. Even better are presentations to departmental or other groups where investigators not directly connected with the work evaluate the data. These exercises require

[1] James D. Watson and John Tooze, *The DNA Story* (San Francisco: W. H. Freeman, 1981), p. 383.

heavy applications of skepticism, the most important ingredient in scientific creativity. As Gerald Holton has pointed out, progress in science is generated by individuals who refuse to accept dogma and thereby develop new constructions that open avenues of research.[2] One must be highly tuned to receive signals from aberrant results.

One of the most repeated excuses given for dishonesty in the research laboratory is the theory of "publish or perish." The end result of the publish or perish syndrome is much more insidious than the occurrence of a handful of fraudulent laboratory incidents. Each year talented young people are lost to clinical investigation because the number of papers published takes precedence over the quality and intensity of the effort expended.

Progress in science is episodic and discontinuous. Thus, over the long haul a creative and persistent investigator is certain to produce new information. However, the pace of discovery depends on vagarious factors. Suppose two equally talented individuals are working on hypotheses, one of which is correct, the other incorrect. There is no *a priori* reason to conclude that one hypothesis is more likely to be correct. In this case, the person with the correct hypothesis will get "results," the other will fail. Thus, in the short run one person appears better than the other, in the long run it will even out. We are in a marathon, not a 100-yard dash! Young investigators must be supported long enough to reach their level of achievement without undue pressure to produce. Since most administrators can only count publications, there needs to be someone in the chain of command who judges the investigator on more substantive grounds, and his opinion should override that of the administrator.

Until now the occurrence of fraud has damaged medical researchers primarily by tarnishing their image, but it has not retarded progress in any substantial way. I believe that efforts to curtail the publication of incorrect results can only effectively arise at the level of individual laboratories or small groups. You will notice that one theme keeps recurring—that of close and active participation in the laboratory by the senior researcher. Dishonesty in research is antithetical and therefore inexplicable, but it can be curtailed. The assembly line mentality and production of results for the sake of publishing only have no place in medical research. The intrusion of governmental and institutional regulatory committees will only retard progress, and the creation of paper guidelines will serve no purpose. The scientific method is self-correcting and no drastic remedies are required. As Pogo said, "We have met the enemy and they are us."

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[2] Gerald Holton, *Thematic Origins of Scientific Thought* (Cambridge: Harvard University Press, 1973).