Reflections on a half-century in the field of transmissible spongiform encephalopathy

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Abstract
The subject of transmissible spongiform encephalopathy may properly be said to have begun with the experimental transmission of scrapie by Cuillé and Chelle in 1936, although Creutzfeldt and Jakob had described the disease that bears their names in 1920-21. Thirty more years passed before the human disease was also shown to be transmissible, in 1966, and the following half century has seen the field move from classical biology to molecular biology and genetics, and from ‘slow virus’ to host-encoded ‘prion’ protein.

Because nothing is more important to the research scientist than the process of seeing a problem and devising ways of solving it, and because we live and die by our publications, as much care should be given to these vehicles of our work and reputations as to the research itself. Four aspects have been chosen for comment: authorship, abbreviations, data presentation, and references.

In addition to the ‘science of research’ there are several ‘para-scientific’ activities that may be categorized as ‘the politics of research’, which include administrative duties, committees (e.g., scientific meetings, grant organizations), journal/book editing, peer reviewing, and public relations. Many young scientists are either unaware or dismissive of the importance of these ‘scientific distractions’, but their potential for influencing the direction of a field of research becomes increasingly evident as careers unfold. They are subject to uses and abuses, and some guidance and examples are given by way of illustration, particular attention being paid to the process of manuscript review which, because of its anonymity, is the most vulnerable to abuse.

As public and government interest in prions wanes in parallel with the disappearance of iatrogenic and variant Creutzfeldt-Jakob disease, the flow of money to sustain research is in evident jeopardy. With an uncertain future, it nevertheless seems possible that one of two things may breathe new life into the field: either an unforeseen new outbreak of human disease will occur (as has happened in the past), or a cross-fertilization between prions and the larger family of protein misfolding diseases, especially Alzheimer’s disease, will bear fruit. For obvious reasons, we should hope for the botanical alternative.

Key words: science, transmissible spongiform encephalopathy, authorship, data presentation, citations.

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Prelude

When this paper was sent to Carleton Gajdusek for factual accuracy and suggestions, it came back with the following note: “I have read your paper. It’s good, but you are too humble. With all the underhanded tricks played upon us we have survived it all intact. I will comment further, later”. Alas, he never did, and this “humble” paper, unencumbered by regrets or bitterness, was presented in gratitude to Carleton, and as a kind of “swansong” lecture at the Prion 08 meeting in Madrid, Spain, in October 2008.

We come to medical research by many different routes, and as often as not we owe it to chance rather than choice. Some of you come trained as physicians, dislocated into research; others come pre-packaged for research with a Ph.D. and only a peripheral interest in medicine. It is a good mix, because it trims the sails of basic research to a course of practical application.

Many of us who entered medical school started out with the idea of becoming neurosurgeons in that self-exalted specialty, but most of us were disabused of the idea within a year or two as we got glimpses of other specialties and found one that pleased us the more. In my case, it was internal medicine, and it happened that in the mid-1960s, the US military knew something the rest of the world didn’t – namely, that the Korean “situation” was going to heat up. They began drafting house officers out of hospitals, and residents everywhere began looking for alternatives to becoming boot camp family physicians.

I asked the advice of Dr. David Bodian, my former neuroanatomy professor, and he suggested I might look up someone at the NIH with an unpronounceable name beginning with G who’d stumbled onto a strange brain disease called kuru in the middle of New Guinea. So I wrote to Dr. Gajdusek, but got no response, and gave up. Four months later, a call came in from the NIH: “This is Dr. Gajdusek’s secretary. He’d like to speak with you”. It turned out that he had been out of the country (I later learned this would be habitual) and that the letter had gone by turns to French Guiana in Africa and South America before winding up in Australian New Guinea. In any event, I traveled 30 miles south to Bethesda and had an interview. Actually, not really an interview – Carleton greeted me at two in the afternoon and was still talking three hours later. Evidently, a capacity to listen was a sufficient criterion for acceptance, and I joined his lab two months later, in 1963.

Science

One of my first assignments was to go to New Guinea to conduct autopsies on patients dying of kuru. I will carry to my grave the memory of removing the brain of a young woman in the middle of a dark smoky hut with the husband looking over my shoulder and pointing out that I had not replaced the cranium quite correctly, and bartering viscera for trade blankets and cans of Dinty Moore beef stew.

The lesson here is to take on whatever opportunity presents itself, because even if we have little or no experience in a given activity, most of us are smart enough to learn quickly to do a creditable job. It is a virtue of youth to be daring, and I must tell you, regretfully, that it diminishes with age. My earliest exposure to scrapie, figuratively speaking, was a conference convened by the US Department of Agriculture in 1964 in Washington. Among the participants were Parry, Gordon, Stamp, and Dickinson. If any of you think the disputes about prions today are acrimonious, you should have witnessed these now iconic figures who had to be restrained from repeated physical assaults over the issue of an infectious versus genetic cause of scrapie.

We are talking of a time when scrapie was the only recognized form of spongiform encephalopathy, was thought to be highly species-specific, and was of interest only to veterinarians, and even then was considered an exotic field of study. After its transmissibility had been proven by Cuillé and Chelle in 1936, almost all of the experimental work on scrapie was confined to Great Britain. However, a possible connection with both kuru and Creutzfeldt-Jakob disease was on the horizon, due in large measure to Polish-born Igor Klatzo, a neuropathologist working at the NIH, who had been looking at kuru brains sent to him from New Guinea by Gajdusek. He wrote a letter to him in 1957, in which he said that the only other disease he had ever seen that looked like kuru was Creutzfeldt-Jakob disease, of which there were then only about 20 recognized cases. He also put Gajdusek in touch with the British veterinary neuropathologist James Innes and his American student William Hadlow, who wrote the now famous letter to The Lancet in 1959 noting the similarity of kuru to scrapie, and suggesting that kuru be studied expe-
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The stage was thus set for Gajdusek to play a leading role, and in 1965 brain tissue from three kuru patients he had inoculated two years earlier transmitted the illness to chimpanzees. There followed an explosion of interest and funding in what were then considered ‘slow virus’ diseases, and over the next 15 years the basic biology, pathogenesis, and epidemiology of nearly the entire family of human and animal spongiform encephalopathies was established. Then, in the 1980s, with the identification of a host-encoded protein molecule closely linked to infectivity, the way was cleared for study of the molecular biology and genetics of these diseases, which continues to the present.

When we begin our careers, we naively think that good, high quality research on significant questions speaks for itself. Surprise! Sometimes it does, and sometimes it doesn’t. There is of course no substitute for a brilliant idea, which is as often as not the product of instinct and intuition rather than reasoned logical thinking. It is thus unpredictable and perhaps even miraculous, and is likely to happen only once in the lifetime of those happy few to whom it occurs.

It is also possible to succeed through sheer ambition – we see this all the time in people who have a single-minded devotion to making money. However, the charge of ambition usually carries a certain pejorative flavor – we speak of people as being ‘overly-ambitious’. Perhaps it’s a matter of jealousy, perhaps not. In any case, if you are bound and determined on getting ahead at all costs, be prepared for some sour looks from your peers.

If, on the other hand, you begin to dream about the importance of your own accomplishments and your claim on just a little bit of immortality, you might want to heed the words of the American novelist Nathaniel Hawthorne in one of his more reflective moments: “It is a good lesson for a man to step outside the narrow circle in which his claims are recognized, and to find how utterly devoid of significance, beyond that circle, is all he achieves”. Or to the even more dramatic pronouncement of the Russian playwright Anton Chekhov: “Here he is in retirement, and now one can see the sum total of his life: not a single page of his labors will survive him, he’s completely unknown, he’s nothing but a soap bubble!”

That’s a little harsh, but in fact most of our work consists of incremental advances rather than major discoveries: a problem is identified, an experiment conceived, then broadened in various ways, repeated, and with luck, a useful bit of new information is brought to bear on an issue of concern to human health and society, which we sometimes forget is the ultimate goal of medical research.

On the other hand, not all research need be goal-oriented. Give a genius carte blanche and something interesting is likely to happen. Wallace Carothers, a brilliant organic chemist teaching at Harvard, was hired by Dupont and given carte blanche to work on his favorite subject, polymers. From this freedom came the unexpected discovery of both neoprene and nylon, which made a fortune for Dupont. A curious footnote to the story is that the letters “nyl” were arbitrary and the “on” was copied from the suffixes of other fibers such as cotton and rayon.

The carte blanche given Carleton Gajdusek during his first few years at the NIH is another excellent example.

I mentioned that good research does not always speak for itself. The benefit of a little self-promotion is implied in that observation, but this can be a tricky business. I think it unlikely that many of you would seek professional public relations help, but it is available, and is known to have been used. Individual taste will dictate how far into this realm it is appropriate to plunge, and it goes without saying that there must be some substance behind the promotion, which is only an adjunct and never a substitute for high quality research.

Because as scientists, we live and die by our publications, it is worthwhile to spend a moment on this critically important vehicle of our research. I could talk at length about putting together a manuscript; making the case for brief introductions, for clarity in such simple but important things as showing results in text, table, and figures in a strictly parallel arrangement, and for including both pro and con arguments in the discussion rather than omitting the cons with a view to promoting an agenda. However, I will limit myself to comments about authorship, abbreviations, the visual presentation of data, and citations.

Authorship

The criteria for authorship are not written in stone – many institutions, including the NIH, run mandatory attendance annual seminars on the subject, and more and more journals are requiring descriptions of each author’s contributions to a manuscript. We also see
papers with the footnote that each of the first two authors contributed equally to the study, reminding us of the adage that we are all born equal, but some more equal than others. In point of fact, there is a perhaps understandable tendency for experimentalists to think that the laboratory results are what really count, and to ignore the contributions of those who furnish their specimens, or put their work into good order. A wonderful pairing of laboratory and literary talent was embodied by the husband and wife virology team of Werner and Gertrude Henle. It is said that she did most of the laboratory work and he did most of the writing and speaking, and together they co-authored many seminal papers that neither could have produced alone.

Three physicians furnish clinical histories on three patients with an unusual phenotype – do they belong among the authors? Absolutely. Fifty neurology professors respond to a request for cases of CJD with two hundred records on patients referred by individual neurologists. Do they all require authorship? The case can be made that they do, and as recently as 2008, Science published a paper on the genome of the rhesus macaque monkey with 176 authors. However, it is more usual for the major contributors to offer collective thanks in an acknowledgment. Does the laboratory technician or animal handler involved in a laboratory transmission study belong among the authors? A question of judgment, but I have included both on numerous occasions. Does your own lab chief, who may not have supervised your work, deserve authorship? Yes, because he has furnished the conditions that allow you to do the work. And so it goes. It seems to me that the best approach can be summed up as generosity tempered by common sense.

**Abbreviations**

Abbreviations are the bête noire of scientific communications. The terminology of prions got out of hand years ago and remains mired in an alphabet soup of confusing and sometimes conflicting abbreviations. We have been treated to PrPc, PrPsc, PrP 27-30, PrP sen, PrPres, PrPu, sPrPsc, rPrPsc, PrPd, and PrPTE, and most recently, in yet another twist of consonants, PSPr, to describe a new proteinase-sensitive subset of CJD. Some of these abbreviations resulted from advances in knowledge, and others were coined anew (or to replace an earlier term) in a kind of ‘proprietary’ spirit. When and if transitional states are identified, we may see PrP\(^+\), PrP\(^-\), PrP\(^\text{iso}\), etc. Editors love abbreviations because they save space; readers hate them because they interrupt the flow of reading. Genetically-engineered mouse terminology is particularly opaque. I have no solution to the problem, but it would repay some serious thought on the part of the molecular genetic ‘creationist’ community, and perhaps it is time to organize a meeting to reign in the present confusion.

**Data Presentation**

It has been said that any original research paper can be completely and succinctly presented in figures and tables, and that it should be possible to understand the study without reading a word of text. An interesting issue is that a figure can be accurate and misleading at the same time (Fig. 1). For example, here is a graph of...
the New York Stock Exchange Index for the months of October and November 2008, showing the stocks in free fall. Notice, however, that the vertical value axis begins at 12,500 rather than zero. If we redesign the graph to show the full value range (Fig. 2), we see that the loss represents just 9% of the total value. Losing 9% of your money is still not a laughing matter, but the graph with the full value range gives you a fairer perspective.

A similar situation can be seen with, say, the duration between an experimentally induced infection and the onset of disease symptoms in treatment and control groups of animals. A graph of one such experiment is shown in Fig. 3. The difference looks convincing – in fact a statistical analysis showed a p value of 0.003. Notice, however, that the horizontal time axis begins at 210 days. When the graph is re-drawn to include the total incubation period (Fig. 4), the increase in mean survival time turns out to be only 12 days, or 6% more than the control.

The following figure has been described as the best statistical presentation of visual data that has ever been published (Fig. 5). It shows the chronology of Napoleon’s ill-fated Russian campaign, with troop strength denoted by the width of the march line drawn on a simple map, beneath which is a parallel time line of ambient temperatures during the long march home. It is clear at a glance that it was not the Russian army that defeated the Emperor, it was the campaign itself: inadequate logistics, starvation, desertion, disease, and Russian weather: he started with nearly half a million troops and returned with fewer than 5000.

### Citations

Lastly, the issue of references. The creation of Internet citation search engines has wrought a minor revolution in scientific research. The ease with which the literature can now be surveyed on a personal computer has virtually depopulated the libraries that in the past were filled with scientists exploring the shelves of journals. You will never experience our frustrations at finding one of every three needed journals already checked out for the next two weeks! In fact, access to the more recent literature is now so easy that many important earlier papers are either unknown or ignored, and in any case judged to be adequately covered by citations of more recent reviews.

Journal editors must also accept part of the blame by virtue of severely limiting the number of references that can be listed. As a result, scholarship has suffered, and has sometimes led to a self-serving omission of highly relevant primary references, or more seriously, to the repetition of work that had already been accomplished, wasting both time and money. An example was recently brought to my attention of a meta-analysis of therapeutic trials of a drug used in cardiac surgery. During a 15-year period there were 64 reported trials: no useful information was added after the 12th trial, and thereafter only a fraction of preceding papers was cited, usually selected to support the results of the new trial. On the other hand, if you begin to think that scholarship is a losing cause in scientific research, you have only to attend a meeting of academicians, and listen to a professor of medieval history talk about his lifelong pursuit of, say, ‘occult religious
symbolism and heraldic shields of the knights of Malta in the latter half of the 19th century”. You will come away with a new understanding of what real paranoia is all about.

Politics

I turn now to what I call the Politics of Research, which may be understood to include the ‘para-research’ activities of administration, meetings, grant reviewing, journal reviewing and editing, relationships with both public and private sources of funding, and contacts with industry and the media.

Administration

One of the more obvious alternatives to research itself is administering the research of others. This may be attractive early in a career, especially a career that seems to be languishing, or it may come later, as with age there is a natural tendency to move further and further away from the front lines of research and take up positions more in keeping with strategic thinking. It may even happen that power and control are more seductive than discovery, in which case administration is a natural selection. I must tell you, however, from personal experience, that administrators today are apt to forget that their primary function is to facilitate rather than control research. Like missionaries who forget they are only intermediaries between God and man, they take unto themselves the aura of holy power. Nevertheless, a really good administrator can be to a research scientist what a really good nurse is to a physician: they can make our jobs easier, more productive, and (not least important) more pleasant.

Scientific meetings: chairs and sponsors

Another means of involvement in the research of others is to organize meetings, or belong to the committee that determines the program. An excellent example is the scientific selection committee of this organization (the European Community Network of Excellence), which determined which studies would be presented orally and which as posters. Numerous other smaller meetings provide similar opportunities.

Granting institutions

Various organizations and foundations continue to fund research in the field of spongiform encephalopathies, and the dwindling supply of university and
governmental money makes the remaining few increasingly important. A committee of research scientists usually chooses which grants to award. Even more than praise and applause, nothing will more endear you to your colleagues than funding their research. Unfortunately, it is best to remain anonymous because the rejected applicants may be seriously annoyed.

Journal reviewing and editing

Journal publications are the lifeblood of the scientific career, and we are all to some extent at the mercy of the competence and integrity of journal editors, their editorial boards, and their stables of reviewers. The privilege and responsibility of reviewing papers written by your peers is certainly the most common means to influence the quality and direction of studies in your field of expertise, but because reviewers are cloaked in anonymity, the exercise also offers the greatest opportunity for abuse.

Editors must be especially careful to maintain a correct distance from active researchers. There is no room in the editorial process for cozy relationships, any more than in the practice of medicine, where physician-patient contacts are held to a strict ethical standard. Some years ago at one of our meetings, the editor of a high profile journal was sitting next to a high profile scientist, and both of them were behaving in a manner that belied a very close relationship. Those who witnessed this episode, and were not among the scientist’s preferred colleagues, essentially wrote off the journal for future submissions. Another more common difficulty arises because of the need to use reviewers who are well informed on the topics under review, who may therefore be in direct competition with the authors. The problem is sometimes resolved by an author’s request not to use specific individuals as reviewers, or by the editor deleting the names of the authors, but this usually only succeeds in making the process a two-way guessing game.

I have heard it said that one reviewer rejects almost every paper he receives, on the one hand because he doesn’t agree with it, and on the other hand because he does agree with it but resents the fact he didn’t think of it first. This is probably just a rumor, but I do know of instances in which the scientist submitting a paper was convinced that one of the reviewers appropriated the information for use in a competitive study. It is equally difficult to substantiate a critique requiring so much additional work as to delay publication until the reviewer can submit a competitive paper. I do not wish to dwell on these matters, because such behavior is extremely rare and, it goes without saying, represents a flagrant lack of ethics.

My own approach is to reject only those manuscripts in which the results are not supported by the data, or which are woefully incomplete, preferring instead to let the editor decide about importance and the readers about quality. In any case, there is no room in reviewing for arrogance, sarcasm, or snide remarks. Be gentle – you are looking at the newborn child of a proud parent, and you should pretend that you are speaking face to face with someone who is easily offended, excitable, and very muscular.

Government, industry, and media contacts

Scientists are called upon by a variety of public and private organizations to render advice or opinions on subjects on which they are considered experts. It is therefore incumbent upon us to act with utter objectivity in giving such counsel, and not to foster a special agenda by creating public concern. The media can be especially troubling because of their vulnerability to dramatic stories rather than factual accounts. An extreme example of this was seen in British tabloid coverage of mad cow disease. However, this should not prevent us from making ourselves accessible and providing the best available information. Responsible journalists keep a stable of favorite contacts in all fields of science, and if you make yourself accessible, you have the opportunity to wield an indirect but important message about the current events in your field.

I can say that I have had almost uniformly good results in dealing with the media through the years, including stories about iatrogenic and variant Creutzfeldt-Jakob disease, as well as about new discoveries in basic science.

Personality

And finally, the importance of personal charm. If no one can deny that the scientific community represents a meritocracy, neither can it be denied that personal charisma wields an influence that is disproportionate to its associated talents. There was, for example, an Institute that is no longer involved in TSE, due chiefly to the death of its charismatic director, who was followed by a succession of good but rather anonymous scientists who failed to maintain the Institute's
Fig. 6. Dr. John Snow’s iteration of all cases of cholera in the London epidemic of 1854.

‘presence’ in the TSE field, and ultimately the assent of its administrative body to continue funding its work. It is also an undeniable fact of human nature that we tend to be gentle towards those we like and harsh towards those we dislike, and this must be recognized and guarded against, just as in granting awards and reviewing manuscripts.

I will conclude with an historical study that at first glance seems to have nothing to do with spongiform encephalopathy, but which in fact perfectly anticipates the current status in our field (Fig. 6). Probably not many of you will recognize this little map, although it represents a landmark event in the history of medicine. It is John Snow’s iteration of all the cases of cholera in the London epidemic of 1854.

He found that nearly all the deaths had occurred within a short distance of the Broad Street pump, and that those few who had lived further away also used the pump. When he brought these observations to the attention of the Board of Guardians, the handle of the pump was removed on the following day. However, after the cholera epidemic had subsided, government officials replaced the handle: they had responded only to the urgent threat posed to the population.

Conclusion

I am fortunate to have seen the study of spongiform encephalopathy emerge from simple classical biology into a complex molecular biology that remains to be synthesized into a new simplicity. Lucky, too, in having had Carleton Gajdusek as my chief, mentor, and friend, whose guiding principle was to allow total liberty to all who worked for him.

The outbreaks of iatrogenic and variant Creutzfeldt-Jakob disease that so excited the public and in consequence stimulated governments to spend vast amounts of money on both basic and applied research
appear to have run their course. Like the aftermath of John Snow’s investigation, public and governmental interest has faded, and we cannot predict where the field will go from here. And yet it seems that every time things quiet down, and we think everything is under control, something new occurs. In the mid-1960s, an entire issue of the Journal of Infectious Diseases was devoted to the question of whether infectious disease was in its death throes as a medical specialty. Within the next two decades there were epidemics of antibiotic-resistant tuberculosis, hepatitis C, and AIDS, and in our own field we have seen three successive epidemics of environmentally transmitted disease. Most recently, concerns have focused on viral respiratory syndromes, including a newly emergent strain of influenza with a combination of avian, porcine, and human genetic elements that recall the influenza strain that killed so many millions of people in 1918 (another subject to which Carleton and I contributed a paper in the 1960s).

It will almost certainly be a good future strategy to emphasize the relevance of spongiform encephalopathy to protein misfolding diseases in general, and to Alzheimer’s disease in particular, as it alone has the cachet and numerical importance to sustain adequate levels of continued funding. I wish you all the best of fortune, and hope that when you reach the end of your careers, you can look back with a sense of satisfaction at a job well done, even if, as the aging American poet Robert Frost wrote:

No amount of having starred
Atones for later disregard
Or helps to make the end less hard...