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SCIENCE AT THE CROSSROADS: FACT OR FICTION?

NAUKA NA RASKRŠĆU: ČINJENICA ILI FIKCIJA?

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Summary: Modern Academic Science is largely based on the formulation of hypotheses that are then confirmed through observations and experiments. There is little scope for *curiosity* that played an important role in early Science. Results carrying negative implications are not easy to publish, and hypotheses have a tendency to take on the mantra of religious beliefs. Academic Science is facing on many fronts pressures that hardly existed in the past. Financial rewards apart from salary can be very high, in the form of fees for consultants, expert legal witnesses, patent development, and even the establishment of private companies. Commercial funding forms a significant percentage of the Total Research Budgets in Science and Medicine, but this often leads to loss of control over research protocols and freedom to communicate the results. Media attention confers fame and prestige that is assiduously sought out by some individual scientists, often supported by University resources, and Press Conferences prior to or synchronous with actual publication. Scientists have long been employed full-time by Government Departments, but research contracts are being increasingly offered by the latter to academic staff on a part-time basis. These pressures and opportunities, together with the priority given to research by most University Tenure and Promotion Committees, are tending to diminish the appetite of scientists for other important responsibilities such as teaching and administration. In a few decades, University scientists have moved from the »Ivory Tower« to the High Street, and many are serving more than one master. The above scenario may bring increased remuneration and the pursuit of research that would be

Kratak sadržaj: Moderna nauka se uglavnom zasniva na formulisanju pretpostavki koje se potom potvrđuju kroz opažanje i eksperimente. Malo mesta ostaje za *znatiželju* koja je na ranom stupnju razvoja nauke imala važnu ulogu. Rezultate koji nose negativne implikacije nije lako objaviti, dok pretpostavke postepeno poprimaju oblik religijskih mantri. Nauka na akademskom nivou suočava se na mnogim frontovima sa pritiscima kojih u prošlosti gotovo da nije bilo. Pored plate, na raspolaganju su veoma visoke novčane nadoknade, kao što su honorari za konsultante, sudske veštake, za razvoj patenata, čak i osnivanje privatnih preduzeća. Komercijalno finansiranje zamenjuje vladine i nekomercijalne izvore, zbog čega se često gubi kontrola nad protokolima istraživanja kao i sloboda da se rezultati objave. Medijska pažnja donosi slavu i prestiž na čijem sticanju pojedini naučnici marljivo rade, neretko uz podršku univerzitetskih resursa i organizovanje konferencija za štampu pre ili u času izlaska publikacije. Naučnici su odavno stalno zaposleni u vladinim ministarstvima, ali ta ministarstva sve češće nude ugovore za istraživanja akademskom osoblju na bazi honorarnog rada. Takvi pritisci i prilike, uz prioritet koji istraživanju daju univerzitetski komisije za mandate i unapređivanje, praktično umanjuju želju naučnika da preuzmu druge važne odgovornosti poput podučavanja i administracije. Za nekoliko decenija, univerzitetski naučnici su se od elite pretvorili u biznismene, pri čemu mnogi od njih opslužuju više gospodara. Gornji scenario može doneti veću finansijsku dobit i omogućiti istraživanja koja bi bez tih spoljašnjih izvora bila preskupa. Ipak, javljale su se i negativne posledice, koje mogu naučnike, ne njihovom krivicom, navesti da postanu saučesnici pri uvođenju lekova i supleme-

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Abbreviations: Caltech, California Institute of Technology; CHD, coronary heart disease; FDA, Food and Drug Administration (USA); LENR, low-energy nuclear fusion; MIT, Massachusetts Institute of Technology; NIH, National Institutes of Health (USA); TV, television; UK, United Kingdom (Great Britain)

too expensive without these external sources, but adverse consequences have also occurred. They may lead to the complicity of scientists, through no fault of their own, in the introduction of drugs and supplements that: a) fail to deliver the benefits claimed; b) increase the risk of some unrelated illness; c) possess dangerous side effects not known or reported at the time of introduction. Examples include hormone replacement therapy and antioxidant vitamins (A and E) to protect against Coronary Heart Disease; dietary fibre to prevent colon cancer; and arguably calcium supplements to treat osteoporosis. On occasions, academic scientists have served as fronts for the publication by the manufacturers of falsified reports minimizing the risk of serious drug side-effects to ensure Regulatory Approval, as occurred with Vioxx in the treatment of arthritis, and Seroquel for schizophrenia and bipolar depression. Individual fraud or misconduct is more frequent than suspected, because most incidents are without major impact and are suppressed by Universities and Funding Agencies. Major scandals are rare, but may have serious repercussions for the general public and bring science into disrepute. Recent examples include: the Cold Fusion controversy (Low Energy Nuclear Reaction); the linkage by Andrew Wakefield of autism with Rubella vaccination; the infamous creation of stem cells by somatic cell nuclear transfer falsely reported by Hwang Woo-Suk. Fraud by commercial companies is subject to the full force of the law, but Science is treated as a self-regulating profession, and as such the punishments handed out are relatively trivial. In essence, Science prior to 1950, except in North America, proceeded along a highway that segregated the traffic into Commercial, Government and Academic streams, and passed through inspiring landscapes and green pastures. It later came to a crossroads from which the alternative road led to the Marketplace, and on which segregation into the above three streams was not enforced. It has now become the main thoroughfare for Science world-wide, but there are reasons to believe that this has increased the incidence of dangerous driving and traffic accidents in the form of conflicts of interest, unethical behaviour, misconduct and even fraud. It may be too late to return to the crossroads and continue along the original highway, but there could be considerable merit in restoring the original segregation between the three streams of Science and in developing, as well as enforcing, a stricter code of behaviour, for which some elements are proposed.

Keywords: scientific fraud, drug development, cold fusion, dietary fibre, hormone replacement therapy, regulatory approval, rubella vaccine, stem cells, antioxidants

nata koji: a) ne uspevaju da ostvare obećani boljitak, b) povećavaju rizik od nekih drugih bolesti; c) imaju opasna neželjena dejstva nepoznata ili neprijavljena u trenutku uvođenja. Neki od primera su terapija zamene hormona i antioksidantni vitamini (A i E) radi zaštite od koronarne srčane bolesti; dijetetska vlakna za sprečavanje raka kolona; i potencijalno suplementi za kalcijum u cilju lečenja osteoporoze. Događalo se da naučnici posluže kao paravan proizvođačima prilikom objavljivanja falsifikovanih izveštaja u kojima se umanjuje rizik od ozbiljnih neželjenih dejstava leka kako bi se obezbedilo zvanično odobrenje, kao što je bio slučaj sa Vioxxom za lečenje artritisa i Seroquelom za depresiju. Pojedinačne prevare ili zloupotrebe češće su nego što se pretpostavlja, jer većina incidenata nema veliki odjek i biva zataškana od strane univerziteta i agencija za finansiranje. Pravi skandali su retkost, ali mogu imati ozbiljne posledice u javnosti i okaljati ugled nauke. Nedavni primeri uključuju: polemiku oko hladne fuzije (niskoenergetska nuklearna reakcija); nameru Andrewa Wakefielda da poveže autizam sa vakcinacijom protiv rubeola; zloglasno stvaranje stem ćelija somatskim ćelijskim nuklearnim transferom koje je lažno prijavio Hwang Woo-Suk. Prevare komercijalnih kompanija podležu sili zakona, ali kako se nauka tretira kao struka koja samu sebe reguliše, kazne koje se dele su relativno banalne. U suštini, nauka je pre 1950, naročito u severnoj Americi, išla putem na kojem je saobraćaj bio podeljen na komercijalni, vladin i akademski, prolazeći kraj inspirativnih pejzaža i zelenih pašnjaka. Kasnije je stigla na raskršće odakle je alternativni put vodio na tržište i na kom podela na navedena tri toka nije bila sprovedena. Sada je to glavni put za nauku širom sveta, ali se osnovano veruje da je to povećalo incidencu opasne vožnje i saobraćajnih nezgoda u vidu sukoba interesa, neetičkog ponašanja, zloupotrebe, pa i prevare. Možda je prekasno da se nauka vrati na raskršće i nastavi prvobitnim putem, ali vraćanje originalnoj podeli na tri toka može vredeti mnogo više, uz uspostavljanje, kao i sprovođenje, strožih pravila ponašanja.

Ključne reči: naučna prevara, razvoj leka, hladna fuzija, dijetetska vlakna, hormonska supstiticiona terapija, zvanično odobrenje, vakcina rubeola, stem ćelija, antioksidansi

Introduction

It is sometimes a good idea to answer a question with another question, in this case:

What exactly is Science?

The most persuasive definition comes from Webster's Dictionary:

The principles and procedures used in the pursuit of accessible knowledge, and involving as necessary conditions the recognition and formulation of a problem, the collection of data through observation and if possible experiment, the formulation of hypotheses, and the testing and confirmation of the hypotheses formulated.

Although it describes very well the way Science has operated until recently at the levels of Funding and Publication, several aspects of this definition are troubling:

1. The exclusive use of the word *confirmation* implies that all scientific knowledge has to be positive, and negative findings do not qualify. This runs counter to the notion that Science is not just the pursuit of ultimate knowledge but of ultimate truth. Some of us know only too well the difficulty in finding a journal willing to accept a paper that reaches a negative conclusion, even when fully supported by sound experimental data. Likewise, Scientific Foundations are not enthusiastic about providing money for research where the investigator expects the outcome to be negative.

2. The necessity of formulating a hypothesis effectively eliminates what, until the late 20th Century, was one of the most inspiring motives for scientific research: *Curiosity*. A simple desire to explore some aspect of the universe was a sufficient reason in itself, and led to many discoveries that are at the very heart of modern Science. This justified Mark Twain's definition of a scientist as:

An individual who satisfies his curiosity at other people's expense.

In today's world such exercises in curiosity are contemptuously dismissed as *Fishing Expeditions*. It is inconceivable that Max Perutz or Frederick Sanger had the foggiest notion what the crystal structure of haemoglobin or the amino acid sequence of the two chains of insulin might be, far less the ability to propose a testable hypothesis, when they sought the funding for their research. The Human Genome Project, arguably the greatest achievement of the biological sciences up to the present, was likewise driven by curiosity and the pure search for knowledge.

3. In hypothesis-driven research, success in competition depends on persuasion that in turn depends on the strength of conviction with which it is proposed. This conviction is necessary before experimental proof and shares many of the elements of religious belief.

Rejection of a self-created hypothesis becomes equivalent to giving up a religious belief and there is a strong temptation to exaggerate the positive and minimize the negative evidence. In this loss of objectivity, the hypothesis takes over its creator as the Monster took over Frankenstein.

Pressures of Modern Times

The practice of Scientific Research in the last two decades has had to contend with new pressures that have brought it to the Crossroads (*Table I*):

Table I Current Pressures Facing Academic Science.

A. Non-Institutional Sources of Income
1) Consultants to Government and Industry
2) Expert Legal Witnesses
3) Patent Development
4) Formation of Private Companies
B. Commercial Funding of Research
1) Major Source for Many Scientists
2) Loss of Control over Conduct of Research
3) Publication Restrictions
C. Fame and Prestige
1) Media Interviews and Press Conferences
2) University Offices of Public Relations
D. Reduced Incentives for Non-Research-Related Activities
1) Teaching, Administration, Professional Excellence
2) Appointment, Tenure, Promotion
E. Increased Role of Government
1) Political Interference: Totalitarian State
2) Full-time Scientists in Government Departments
3) Government as Contractor
4) Space and Defence Programs

A. Financial Pressures have taken many forms. The rewards of scientific success have never been greater, at a time when failure has never been so severely punished. One only has to count the number of New York taxi drivers who hold PhDs. This is not simply a matter of remuneration for a job well done. Great wealth can be earned by developing a patent. Most academics are permitted to act as highly paid consultants to commercial companies or as expert witnesses in legal cases. Staff at some of the most prestigious American universities have been allowed to form their own companies that have later been launched on the Stock Market or bought out by other enterprises. Curiosity and the search for true knowledge have been overtaken by that most magnetic of motives, money.

B. The partnership between Science and Industry has been of incalculable value to both. How many additional centuries might it have taken to reach our present state of knowledge without the superb instrumentation and equipment available for contemporary research? What percentage of a scientist's time would be taken up in reagent preparation were it not for the excellent reagents, analytical kits, monoclonal antibodies, plasmid vectors and antisense constructs that can be had for a glance at a catalogue and the price of a phone call? How could scientists cope with the tidal wave of new information and access the past if they did not have computers and programs in their offices and laboratories? Conversely, one has only to check the names of companies listed on the New York Stock Exchange and their profit records to appreciate how evenly balanced the benefits have been.

Commercial Funding plays a prominent role alongside Government and Non-Profit Foundations in providing financial support for University-based research. In Canada, data for the first decade of this millennium reveal that Commercial Funding averages

12–16% of the Total Annual Research Budget for all faculties combined. These figures include support for Arts and Humanities, faculties that do not usually attract Commercial Funding. Of the 99 Universities included in the survey, only 18 include a Medical School which typically is the recipient of generous support from the Pharmaceutical and Health Care Industries. The contributions to Science and Medicine are difficult to segregate, so that the percentage of Commercial Funding to these faculties as a percentage of the total institutional budget is diluted by the amounts from taxpayers and charitable donors on which the other faculties mainly depend. The situation in USA is likely to be similar, since Canada has generally been condemned to imitate the behaviour of its larger southern neighbour. Regrettably. Commercial Funding may lead to all kinds of dubious practices, from control by the company over the way the research is conducted and communicated, to outright fraud in some cases where external scientists of some distinction have been paid to add their names to a paper entirely written by the company's own staff (1–3). It has also dampened enthusiasm for teaching, administration, and other activities for which Universities are primarily founded and funded. Some attempts have been made by Academic and Health Care Institutions to draw up guidelines to regulate contracts between individual scientists and commercial companies, but these are poorly monitored, weakly enforced, and rarely are breaches punished.

C. Fame and Prestige await the successful scientist as never before. Science and Technology have contributed so much to human survival, welfare, and pleasure in the last 100 years that a grateful public eagerly looks forward to the next great discovery. Press and Television assiduously feed this appetite, but not always with the desirable degree of accuracy and responsibility. Once, after a presentation at an International Meeting, I was greeted by the correspondent of a National Daily newspaper who bombarded me with the most basic of questions, to the point where I asked if I had the pleasure of addressing the Science Correspondent:

»Oh no« she replied. »I am the Dance Correspondent. Our Science Correspondent does not work at week-ends«.

There is nothing wrong with an investigator discussing his paper the day of its appearance in *Science* or *Nature*, after being approached by the Media; but it is a very different matter when, overwhelmed by the desire for public acclaim, he is the one who takes the initiative. Yet nowadays, Press Releases, Press Conferences, individual Radio and Television interviews often precede publication, although some journals prohibit such premature self-advertising. Most Universities have well-staffed Offices of Public Relations to help in this publicity. The announcements always carry the warning: *These results are preliminary and require further investigation*. One is also reminded of the ubiquitous telephone message that greets most calls to commercial or Government offices: *This call will be monitored for quality control purposes*.

Priority in discovery or publication is central to success in science, and speed is the dominant requirement. After all, there is no punishment for being wrong if no dishonesty was involved, and potentially great rewards for being right even if it only happens once in a lifetime.

D. Academic Progress such as Tenure and Promotion has more to do with the perceived quality of the candidate's research, usually measured by the number of papers published and the amount of financial support received, than any other activity. Selection Committees choose brilliant investigators and their collaborators in preference to distinguished teachers. The temptation exists for the most intellectually gifted academics to focus on research at the expense of their teaching duties. Recently, an American company was established for the purpose of marking and grading student assignments and examination papers, which are sent to Universities in India, Singapore, and Malaysia charging modest fees for this service (4). The idea imitates the offshore offloading that is now a feature of the computing industry, but it is sad to see this principle applied to the sacred relationship between student and teacher.

The pressure to succeed in research can lead to dubious practices or, on rare occasions, outright fraud (5, 6). Sometimes, use is made of the peer review process to plagiarise, to discredit or to delay the progress of competitors (7–9), although more commonly congenial relations are the rule among scientists working in the same field, unless that field happens to be *Climate Change*. A practice that has been well documented but difficult to prove definitively takes the form of omitting references to earlier work in order to inflate the novelty value of the paper submitted. In many such cases, it is not always possible to draw the line between plagiarism and ignorance, and in those that do actually make it into print, the referees are as ignorant as the authors (10, 11).

E. Political Interference in science is rare in a democracy, but not so rare in a totalitarian state. Flagrant examples include the human experiments carried out at the Nazi Death Camps, and the use in Soviet Russia of psychiatrists to certify dissidents so that they could be locked up out of harm's way. Most extreme of all was the imposition of Lysenko's Theory of Environmentally Acquired Inheritance as the only acceptable basis of Genetics in Stalin's Russia and Mao's China. Mendelian Genetics were banned and its exponents were driven from their posts in Universities and Research Institutes (12). The Agricultural

productivity of these countries suffered devastating consequences through the implementation of politically motivated notions that the scientific and educational establishments had to accept by government decree.

A different facet of Science and Government working hand in hand was evident in the Two Great Wars of the last century and the many minor wars that followed them, leading to the development of chemical and biological weapons, and ultimately the atomic bomb. Espionage departments have their fair share of scientists, and are alive and well to this day. The technological spin-off from these activities has been enormous. One only has to think of the advances in telecommunications, transportation, energy production, meteorology and computing that originated in the back room of some military department — Departments of Defence I think they are usually called. How many of the devices on which we depend so much in our daily life would have had to wait decades and even a century or so to see the light of day had it not been the driving force of military necessity that forced them to a premature birth. The World Space Program is entirely the creation of Governments and the scientists who work on their behalf. Private industry acts in the capacity of sub-contractor, and only has a small role in developing initiatives of its own.

The success of these programs has been very easy to confirm unambiguously. It is known within minutes of happening whether a space mission has reached its destination or has exploded on the launch-pad. The birth of a hurricane and its subsequent progress can be predicted with great accuracy, although the human responses to these threats sometimes fail to reap the benefit of this scientific information as occurred with the *Katrina* disaster in USA.

In the sphere of *Climate Change*, science is on shakier ground, while still under pressure from Governments who are paying the bills, and ideological pressure groups who have a vested interest in using a worst-case scenario as a means to redistribute wealth and economic power from the *have* to the *have-not* nations of the universe. Skulduggery such as muzzling the competition, and statistical manipulation have been revealed by the so-called *Climategate E-Mails* (13–15), even though those involved have been surprisingly exonerated by the three committees that reviewed the evidence. The more pernicious aspect of this controversy is not whether Climate Change is taking place – it probably always has in one direction or another since the earth was born – but whether the most recent rise is caused solely by human activity, and whether the measures proposed will succeed in halting or reversing the process. These last two questions can easily be answered by economists and politicians on the basis of conjecture and intuition (and who in light of our current financial disasters would trust either?), but they can only be answered with reasonable certainty by scientists through the design and execution of experiments to test their hypothesis, and to demonstrate that the proposed solutions will work in a model that simulates the conditions predicted if nothing at all is done. This has yet to happen, and so far nobody is proposing to do anything about it.

Consequences of These Pressures

The factors described above have ambivalent consequences. They can be forces for good in stimulating scientific excellence by enhancing the motivation of individual scientists, encouraging collaboration, and providing the resources for research whose costs are way beyond the norm and would otherwise be impossible to pursue. But they can also be harmful in several ways (*Table II*):

A. They may lead to the introduction of drugs and supplements that

1) fail to deliver the benefits claimed

2) increase the risk of some serious but unrelated illness

3) possess dangerous side effects not known or not reported at the time of introduction.

The assumption is that these consequences came about because of flaws in the science or in the referee and publication processes, and not as a result of deliberate fraud. The *thalidomide* disaster is a case in point, and its recent reintroduction as an anti-cancer agent is one of the Cinderella stories of modern investigation (16, 17). Other examples include:

Table II Adverse Consequences of these Pressures.

A. Introduction of Undesirable Drugs or Supplements
1) Failure to Deliver Benefits Claimed
Dietary fibre for colon cancer; Vitamins A & E for CHD
2) Unfavourable Interactions with Other Drugs Being Used
3) Unpleasant or Dangerous Side Effects
• *Hormone replacement therapy for CHD;*
• *Calcium supplements for osteoporosis*
4) Unexpectedly Cause a New Disease
• *Thalidomide birth defects*
B. Misconduct and Fraud
1) Initiated by Commercial Companies With Complicity of Academic Scientists
• *Use of Vioxx for treatment of arthritis*
• *Seroquel for treatment of bipolar depression*
• *Nexium scandal*
2) Initiated by Academic Scientists Independently
• *Cold Fusion (Low Energy Nuclear Reaction)*
• *Linkage of Autism to Rubella Vaccine*
• *Creation of stem cells by somatic cell nuclear transfer*

a. *Hormone Replacement Therapy* to protect against Coronary Heart Disease in post-menopausal women. It is now established that this may actually increase the incidence of heart attacks and strokes in the population being treated (18, 19).

b. *Calcium Supplements* to treat or prevent Osteoporosis. Not only do these have little if any beneficial effects on osteoporosis, in contrast with natural dietary calcium; a recent meta-analysis has shown a 30% increase in CHD and stroke among those treated (20).

c. *Dietary Fibre* to prevent Colon Cancer. Initial epidemiological data showed an inverse correlation between fibre intake in regular diets and colon cancer, but reduced incidence could not be established among those taking fibre supplements (21). More recent investigations have failed to show even a positive effect of fibre in the diet (22, 23), and it is probable that persons who spontaneously take a high fibre diet are better educated and live a healthier life style than those whose natural diet is low in fibre (24). Like wine consumption (25), dietary fibre may simply be a marker for good habits. Exactly the same considerations apply to the *Antioxidants, Vitamins A and E*, that for long periods were recommended for the prevention of CHD (26–28).

The above three case histories are representative of many others of a similar nature that occur from time to time, especially in the field of Nutrition. The consequences are not always harmful but they provoke the following concerns:

1. There is always money to be made by someone, usually manufacturers and retailers, out of the particular dogma being promoted, and therefore the prospect that some of the supporting research stems from conflicts of interest.

2. Hungry and uncritical media sources frequently sensationalize the reports, and the bandwagon effect makes it difficult for those who do not subscribe to the dogma to refute the original claims.

3. When the refutation finally comes, the General Public is left in a state of confusion that generates a cynical attitude towards science as a whole.

B. The second category includes those instances where manufacturers, with the complicity of apparently independent scientists, deliberately promote products that knowingly do not possess all the beneficial properties claimed, or minimize their dangerous side-effects. Issues of this kind are more common in the Chemical and Pharmaceutical Industries than any other, and have been facilitated by external scientists willing to allow their data to be manipulated because they have legally signed away control as part of their contracts with the company, or who sign off as authors although the work was carried out by the company's own employees.

Scores of examples of this phenomenon have come to light in recent years. Only three such cases will be mentioned:

1. *Use of Vioxx for Treatment of Arthritis*. In 2004, the manufacturers, Merck, withdrew this drug because of impending lawsuits (29). Over the next 2 days its stock exchange value dropped by 25 billion dollars. More than a year thereafter, the New England Journal of Medicine published an editorial (30) critically examining a crucial paper favourable to the drug that it had earlier published (31), and pointed out instances of fraud on the part of the authors and the manufacturers in the way the data had been selected and presented. The sluggishness of this action and the faulty reviewing standards that it revealed ignited a storm of condemnation, especially in light of the estimate by FDA analysts that Vioxx caused between 88,000 and 139,000 heart attacks, 30–40% of which were probably fatal, in the 5 years during which it was marketed (32, 33).

2. *Use of Seroquel for Schizophrenia and Bipolar Depression*. After gaining FDA approval and being released by AstraZeneca with considerable success, it became clear that this drug increased the risk of Type II Diabetes 4–6-fold, and an unexpected number of patients developed acute pancreatitis. It subsequently emerged that these complications had turned up during development but the information was omitted from the papers submitted for regulatory approval (34, 35).

3. *Nexium in the Treatment of Gastric Acidity*. This episode also involves AstraZeneca. It has little to do with side effects and much to do about marketing. The company had produced a highly successful acid suppressant, Losac, that contained equal amounts of two enantiomers of the same compound, R-omeprazole and Esomeprazole. Both are converted by gastric acid to the active agent. When the original patent was about to expire, Nexium, comprising only pure Esomeprazole, was introduced as a much superior drug at a much superior price and under new patent protection. Little money was required for its development, but a great deal was spent on its promotion, mainly to medical practitioners by sales staff who sold the notion that Losac was not all that good after all, and Nexium was the new gold standard (36). In line with scientific expectation (36), it has been hard to demonstrate any real difference between the drugs apart from price, now that Losac can be sold generically. It should be recognized that many qualified scientists and physicians are to be found in the Marketing Divisions of the major pharmaceutical companies, playing a role in policies and procedures and how they are practiced (2).

C. The final category comprises the most blatant instances of fraud carried out by individual scientists entirely on their own initiative and for their own personal advantage, although outright financial gain was usually not the primary motive.

1. The *Cold Fusion* episode represents a controversy as much as a fraud, since the issue is still being debated to this day (38, 39). It started with the dramatic claim by two individuals, Fleischmann and Pons, the first an Englishman, the second an American, that they had successfully carried out nuclear fusion at room temperature. The evidence they cited to support this claim rested upon an increase in overall energy within a closed system, and detection of activated neutrons and tritium characteristic of a nuclear reaction (40, 41). This phenomenon of a *Low Energy Nuclear Reaction* could not be explained by the current Laws of Physics, and it was not surprising that hardly anybody could replicate these results, although there were some positive claims to this effect. Subsequently, Fleischmann and Pons retracted the claim that they could detect nuclear reaction products although they still insisted that their system could generate an unexplained increase in overall energy. But an explosion of interest had been created by the Press Conference given by the two scientists shortly after their paper was published and the achievement was praised beyond all proportion in broadcasts and news reports throughout the world. Several Governments contributed significant funds for further research into this issue and a number of journals and an international society dedicated to the concept of LENR sprang into being to promote what has now come to be called *The Fusion Confusion*. The US Academy of Sciences has held no fewer than three conferences on the topic over the last decade, all of which concluded that no convincing evidence has yet been provided that justifies support for LENR.

2. The next incident, *The Linkage of Autism with Rubella Vaccination*, was exclusively of British origin although the regrettable repercussions have been world-wide. A gastroenterologist called Andrew Wakefield took 12 blood samples from children attending his son's birthday party, paying each of them 5 pounds, and proceeded to write a paper that was published by the Lancet in 1998 claiming that many cases of autism were caused by Mumps/Measles/Rubella vaccines (42). He spent much of his time subsequently appearing as an expert witness in a series of cases where parents with autistic children sued the manufacturers of the vaccines. The Media gave enormous credibility to this story. Over the next few years, a powerful campaign against vaccination was launched, led by Wakefield and families affected by autism. Vaccination rates fell from over 90% to less than 50% in many countries, followed by Rubella epidemics. Fear of all forms of immunisation spread, leading the WHO to warn of the serious risks to Public Health. Throughout this period, many reputable investigators failed to confirm the linkage in large populations, and other evidence against it accumulated. The true nature of Wakefield's data became known (43). It took the Lancet 12 years to publish a retraction (42), followed by retraction of a second related paper by another journal (44). The British Medical Council barred Wakefield from medical practice (45), but by then he had moved to an American University that supported his work. Angry parents staged protests, claiming that their hero was a victim of persecution by the orthodox medical establishment. It seems that scientific fraud is one of the few crimes that can generate unexpected public support for the criminal.

3. Some elements of this scenario are being repeated, again with Media complicity, in the so-called *Liberation Therapy for Multiple Sclerosis* promoted by the Italian Dr Paolo Zamboni. He has published findings that venous narrowing in the brain accompanied by iron deposition is the likeliest cause of the disease (46–48). Although at least four unpublished studies have failed to confirm his results, including one from Sweden and another from Germany, Zamboni has gone ahead with an operation to relieve these constrictions (49–51), and has publicized his success through Press Conferences, and the publication (with or without his prompting) of stories about patients who have come forward claiming to have been cured by his techniques. Clinics offering these expensive procedures have sprung up in several countries, and there is no shortage of desperate patients banging on the door for admission. Those qualified scientists who criticize the small numbers and uncontrolled protocols in the written and verbal reports also do so in media outlets. They, and the politicians and directors of Multiple Sclerosis institutions who advise caution, and the need for much more extensive work before adding the burden of these procedures to the back of the taxpayers, are publicly abused by unfortunate but angry patients who cannot afford this treatment. We are likely to see many more scientific issues fought out in this arena, and the only ones who are certain to benefit are the proprietors of newspapers and TV stations.

4. The *Fabrication of Cloned Human Embryonic Stem Cells* by the Korean biologist Hwang Woo-Suk must stand as the most audacious and outrageous fraud yet perpetrated in any scientific field. His work, initially reported by Science in 2004 and 2005 (52, 53), but subsequently retracted by the journal, won universal acclaim and made him a national hero rewarded by many honours, including the creation of his own personal research institute, the issue of a commemorative postage stamp, and large sums of money. Gradually, rumours emerged challenging the ethical standards of the research, alleging large payments to staff and students for egg donations, as well as embezzlement of research funds by him and some of his associates (54). This unleashed a storm of street protests in favour of Hwang as well as the support of the Prime Minister and many influential politicians. Things became more serious as some of his co-authors broke ranks and admitted that the

stem cells had actually been fabricated. These charges were met by loud denials from Hwang and even louder demonstrations of support by the citizens of Seoul. After a police investigation and overwhelming evidence of fabrication testified by Korean and International experts, he was indicted for embezzlement, violation of ethical laws, and fraudulent stem cell research. At his trial, he received a 2-year suspended prison sentence for the first two offences but was cleared of the third (55, 56). Throughout this period and since, he has published 40 further papers, all of them listed in Pub Med. It is astonishing how readily scientists are forgiven their sins (57).

Crime and Punishment

The issue of how science should be conducted is not trivial. On September 16th 2010, there were 3861 citations under the heading *Scientific Fraud* and 3724 under *Scientific Misconduct*. A short way behind came *Nobel Prize* with 3432 citations, emphasizing that the good just about cancels out the bad. A recent review reported that 2% of scientists admitted to outright fraud at least once, and 34% to other questionable practices (58). Of the same respondents, 14% claimed to have observed fraud among colleagues and 72% other questionable practices. In a later report, 53% of those observing either form of behaviour intervened, and their intervention resulted in a satisfactory outcome in 40% (6).

There is probably no country in the world that has a Code of Criminal Laws governing Scientific Research. It is largely beyond the reach of the Law and operates as a Self-Regulated Profession. In most of their activities, industries such as Banking, Finance and the Stock Market are also self-regulated, and we all know what a mess they have made of things in the last few years. A cynic might say that the Mafia is one of the oldest self-regulating professions and the Mexican Drug Cartels one of the newest. Nevertheless fraud may have some unpleasant consequences for those who perpetrate it, although these vary greatly with the circumstances (*Table III*).

A. *Corporate Fraud*

Where fraud or misdemeanours committed by a corporation results in perceived damage, the persons harmed can take legal action through the Civil Law either individually or in Class Action Law-suits. The total sums of money awarded in damages can be in the billion-dollar range, and the stock market value of the company will be adversely affected. While the company as a whole is subject to retribution, the individuals responsible are generally not liable to Legal Action. Presumably, they are dealt with internally by the company, although even this is doubtful (2). The FDA has failed far too often in its role as regulator of the pharmaceutical industry and seems at time to be more intent on protecting the interests of that industry than the health of US citizens. On the other hand, that industry is prone to flex its financial muscles through lawyers and lobbyists to intimidate and silence its critics (2, 59, 60).

Table III Punishment for Fraud and Misconduct Outlined in Table II.

A. Corporate Fraud
Subject to Civil Litigation and Occasionally Criminal Investigation

- *Can have devastating effect on company's profits and stock-market value*

B. Academic Fraud
Subject to Self Regulation by Universities and Funding Agencies

- *Punishment inversely related to seniority of perpetrator*
- *Correction, resubmission, withdrawal or retraction of affected papers*
- *Removal from Grant Review Panels, usually for limited periods*
- *Disqualification from applying for research funds: rare, and usually for limited time*
- *Dismissal: very rare for professorial staff*

B. *Individual Fraud*

While theoretically such persons are open to Civil Lawsuits, this rarely happens because you cannot take from someone money that they do not possess. Retribution is left to the bodies (Universities, Hospitals and Research Foundations) that supported the fraudulent work through employment or grants. These exercises in Self-Regulation fall far short of the level of retribution required as a realistic punishment or deterrent. It is not hard to see why this is so (61).

1. Universities may originally have been established to spread truth and knowledge, but *Self-Interest* soon joined the ranks of these lofty ambitions. Simply put, nothing scares a University administration more than a good scandal, and nothing can be more scandalous than scientific fraud committed within its holy precincts (62).

2. When the fraud occurs at a high level, those who first become aware of it are likely to be graduate students or post-docs (6). It takes a lot of courage to approach the perpetrator, and the courage of a saint to go beyond this to higher authority (*Tables IV, V; Figures 1, 2*). If the discovery is made by a collaborator or co-author of equal or higher status, the matter is usually settled within the immediate family by omitting or restoring the questionable data (61). If the paper has been submitted or published, a *correction*, *resubmission*, and in extreme cases *withdrawal* or *retraction* usually works. Even when the matter is reported and an internal review agrees that fraud has

Table IV Number of incidents of scientific misconduct observed by 1599 respondents to a questionnaire. *Data extracted from Ref. 6.*

Type of misconduct	Numbers
Fabrication and falsification	610
Questionable publication practices	600
Plagiarism	450
Incompetent data analysis	420
Careless record keeping	330
Internal bias and rigging results	190
Dishonesty (including use of funds)	170
Ethical violations	160

Table V Outcomes of intervention in 1599 suspected cases of suspected scientific misconduct. *Data extracted from Ref. 6.*

Outcome	Percentage of total cases
1. Suspect Corrected Problem	28
2. Concern Unwarranted	14
3. Suspect Denied Problem	27
4. No Way to Correct Problem	13
5. Suspect Did Nothing to Correct Problem	20
6. Suspect Did Not Respond to Intervention	10
7. Elevated to Local Office	20
8. Elevated to Federal Office	8

been committed, the steps described above are usually deemed sufficient to resolve the problem (63).

There have been many instances where the fraud is suspected by the Panel that awarded the research funds, most commonly NIH, and an external review confirms this to be so. The punishments handed out by the agency include banning from membership of a Review Panel for a number of years (usually 3 to 5). To this may be added disqualification from holding a Grant from that agency over the same period. Very rarely, these restrictions are for life. It is almost unheard of for a tenured academic staff member to lose his position for even the most flagrant misconduct.

3. Fraud at lower levels involving *non-tenured staff* such as graduate students and post-docs is more harshly treated (62), although not always so. Outright dismissal is not uncommon, but if the accused puts up a fight or threatens legal action, some compromise is usually found: anything in fact to avoid publicity that may damage the institution concerned.

What Road Should we Take?

In retrospect, it seems that science in the 18th and 19th Centuries was a much more gentle sport

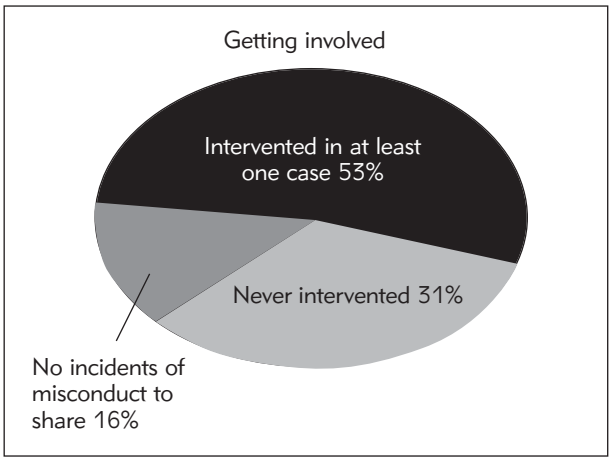

Figure 1 Reaction of colleaques to observation of suspected scientific misconduct. Data are percentages based on 2599 responses to questionnaire. *From Ref 6, with permission*.

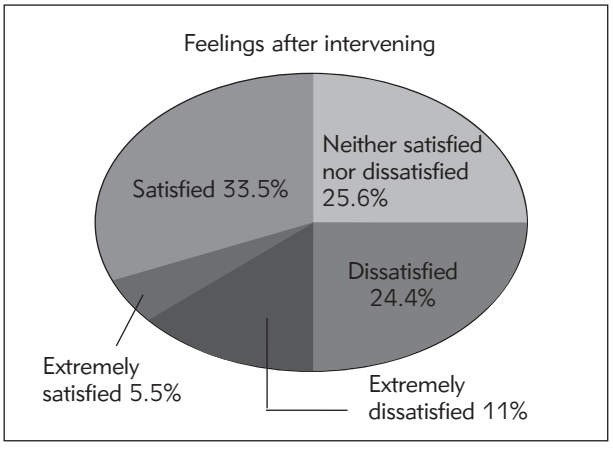

Figure 2 Feelings of those who intervened in above cases of suspected scientific fraud regarding final outcome. *From Ref 6, with permission.*

than in today's fiercely competitive world. This may be a mere illusion, fondness for an era we can never know but only imagine. However, I think that I have shown that the road we are presently on contains many pitfalls and dangers, and we should at least be open to the possibility of reaching our destination by a more pleasant route. That road does in fact exist, but mainstream science parted from it half a century ago. It offered much more freedom and security than today's overcrowded highway.

The road I want to describe, the Science Superhighway of the 1950's and 60's had three lanes, each marked by double-yellow lines that could not be crossed, except in occasional stretches of dotted lines. The outside one carried Commercial traffic; the middle Government traffic; and the inside lane, the slowest, widest, and safest was for those drivers whose licence plates were stamped *ACADEMIC FREEDOM*. It offered a more leisurely journey, but the spectacular land-

scapes and green pastures dotted with Ivory Towers offered adequate compensations. A graduating scientist had to choose between these three options and changing lanes was not an easy matter. For those who selected the Academic Lane, everything required for steady progress was provided. An academic position came not only with a salary, but a suitably equipped laboratory and a basic complement of technicians, graduate students and post-docs. The money for these amenities came directly from the central budget of the university, mostly provided by the Government but supplemented in some cases by donations and endowments. There was no need to write a single Grant Application to receive this level of support, but at the end of 3-year or 5-year periods, the scholarly achievements of the individual were externally evaluated and the level of support adjusted accordingly. For those who wanted more gas in their tank, there were a number of foundations that could be approached on a competitive basis. The application process was simple, and depended more on past performance than anything else. New investigators lacking a track-record were usually given the benefit of the doubt in the form of seed money to get them started.

One principle was rigorously enforced: academic staff were not allowed to receive remuneration beyond their salaries. They were free if they wished to act as consultants to Government and Industry, or as experts in Court, but they were not encouraged to do so, and any money earned had to be turned over to their University Departments. The situation I describe was that with which I grew up in UK. It applied with minor variations in Europe and the British Commonwealth, but was very different from the system in USA. Not only were American Academic Scientists required to raise their research operating expenses from Grants. Many were expected to obtain part or even all of their salary from this source or from Commercial sources. These two roads have now intersected to create the *Cross Roads* of my title. It is a very dangerous junction. Traffic on the US Superhighway is getting heavier and heavier as the spirit of the entrepreneur is threatening to extinguish that of the scholar. No profession that expects and requires its practitioners to have one hand in the till can escape without blemish or indignity. Those who take this route, that is inadequately regulated relative to the volume and variety of traffic it has to carry, eventually traverse the High Street and end up in the Market Place.

Can we retrace our steps and return to the Science Superhighway? It would require a huge U-turn posing serious dangers of its own. There is a safer alternative, but its implementation would require a great deal of courage and idealism, qualities that, sadly, are in short supply in our dangerously materialistic world. Only a well-regulated system limiting the options of individuals and institutions would bring the combination of security and opportunity within a framework of high ethical standards that characterized the operation of Science in previous incarnations; but this runs counter to the free-market philosophy and self-indulgent libertarianism that dominate our era (*Table VI*).

Table VI Recommended Rules of the Road.

A. Remain the Servant of One Master
B. Decline External Work and Commercial Contracts
C. Provide Adequate Research Resources to Academic Staff
D. Limit Staff Size of Individual Investigators
E. Simplify Grant Application Processes
F. Create National or Regional Office of Research Ombudsman

Recommended Rules of the Road

1. The Servant of One Master

The notion of a full-time tenured academic position being a job for life should carry with it the corollary that the holder of such a post devotes all of his working time to that University for as long as his employment endures. Since Government scientists carry the same privileges, the same notion can reasonably be applied to them.

The commercial world operates under different rules, usually for much higher but less secure rewards. The logical outcome would be to restore the barriers between the three main research streams that used to exist and reduce the potential for conflicts of interest, arguably the most persistent and pernicious motivating factor in scientific misconduct (64, 65).

2. External Work and Commercial Contracts

These activities should not be encouraged, and should be permitted only where they are likely to enhance the personal research of the scientist involved. Any remuneration should pass directly to the University and not to the individual. All such work would have to contractually guarantee the total academic freedom of the participant.

3. Provision of Adequate Resources

In addition to a salary and a laboratory, academic staff, from their first appointment onward should be provided with sufficient personnel (technicians, graduate students, postdoctoral trainees) to allow them to function independently of external grant support, although applications for the latter should be encouraged. It is remarkable that academic science represents about the only public service where the incumbent is expected to function without the resources enabling him to do so being provided by the employing authority.

4. Limitation of Staff Size

Just as each scientist should have a minimum staff to ensure that they will be able to perform research in the course of their employment, there should be limits on the total number, especially where students and trainees are concerned. Like alcohol, too much can be as undesirable as too little. There is a clear trend among some scientists – the prompting of ambition or the reward of eminence – to build up big research operations on a factory scale. There is also a tendency to recruit graduate or postdoctoral students in preference to technicians who cost more in salaries and benefits, and whose conditions are regulated by Institutions or Unions. Technicians work predominantly for the *boss*, whereas Students are more directly advancing their own careers and are more likely to work all the hours demanded, even when the demands are unreasonable; they also have literary and bibliographical skills that are rare among technicians, and are frequently involved in the writing of papers and grant applications. The other side of the coin is the obligation of their supervisor to provide scrutiny, guidance and tuition, as well as advice and encouragement. These obligations do not work well when the group becomes too large. It is not a co-incidence that more episodes of fraud and misconduct have been attributed to graduate and postdoctoral students (6), especially under circumstances of poor supervision.

5. Revision of Grant Application Processes

It is important that the peer-review process be thorough and scrupulous for scientific publication. This is not always the case. It is less important that eminent scientists spend endless hours reading extensive grant applications and the reams of appendices and papers (published and unpublished) that accompany them; preparing their reports; and spending several days annually in the company of equally eminent scientists who have done exactly the same thing to decide who should, and who should not, get the money. The overall costs in time and resources are mind-boggling. There is little accountability for how the money, if awarded, is actually spent. In some cases, the work has already been surreptitiously performed before the grant is submitted. Several cases of plagiarism by reviewers have been established by NIH investigations, the only retribution being removal from the Review Panel – a punishment that many might welcome. It is time to put a stop to this waste in favour of a process that asks less of all concerned and minimizes the mindless bureaucracy of most funding agencies. The track-record of the applicant and the relevance and potential importance of the proposed investigations should be the paramount considerations. These issues can be adjudicated with a fraction of the current human and financial costs by radically simplifying the present system. Applicants, Universities, Funding Agencies: all would be winners.

6. Office of Ombudsman

When scientific misconduct is thought to occur, there is no well-defined instrument for its investigation. *Ad hoc* procedures spring into existence varying from one institution to another (66). Within the institution, there tends to be a closing of the ranks to protect its reputation, if not that of the person under suspicion. The issue becomes external only in extreme cases, and in some may involve the intervention of government departments, professional organizations, and funding agencies, individually or collectively. Different groups may well reach different conclusions. The first David Baltimore scandal that focused upon an academic colleague and a post-doctoral trainee took a sequence of committees and a decade of time to reach a final resolution in his favour (67). One of the ironies of the case is that while his colleagues at MIT were solidly supportive, those upstream at Harvard were calling for his head. The second, many years later at Caltech in which a graduate student was at the centre, resulted in his absolution in no time at all.

The anomalies that plague *ad hoc* committees established to review scientific misconduct are further illustrated by the composition and operation of those set up to investigate the Climategate affair and that have reported their findings that essentially exonerate those under suspicion of misconduct. Two were established by the University of East Anglia, home of the Climate Research Unit and its director Dr Phil Jones who was at the heart of the scandal. The first was chaired by Lord Oxburgh who is known for his business interests in wind farms and green capital investment firms. Although it was initially intended that the material to be examined was to be selected by the Royal Society, it was actually submitted by the University with the approval of Dr Jones. The second committee was chaired by Sir Muir Russell, and was more concerned with behavioural aspects of the case. Jones was surprisingly cleared of perverting the peer-review process mainly on the basis of his own assertions. The issue of breach of Freedom of Information Legislation (FOIL) arising from the deliberate deletion of e-mails that might be subject to such enquiries from the Press and those scientists with contrary opinion was not even discussed in the final report. The membership of both committees virtually excluded any climate change sceptic, and e-mails obtained by access to FOIL by the press revealed a vigorous campaign by the climate change lobby to achieve this very goal (68, 69).

The notion of establishing a permanent external watchdog is not new. The Division of Investigative Oversight of the US Office of Research Integrity has been established for this purpose (70), but its terms of reference have made certain that it is a watchdog with a tight collar, a short lead, and no teeth, that can only sniff around the backyard at the behest of the Institution. Even this toothless canine has triggered resentment and the charge of undermining academic

self-governance (71). It makes sense to have an expert with the required resources, and a standard set of procedures, available to look into allegations of misconduct. This person could be approached not only by the institution following an internal complaint, but also directly by the individual(s) making the allegation, where fear of reprisal or of a biased investigation might deter internal reporting of the event. Such individuals frequently go under the derogatory term *whistle-blowers*, but there are circumstances in which blowing the whistle can come to represent a heroic act in defence of scientific truth and justice (72).

Conclusion

The subject matter of this presentation does not lend itself to strict objectivity, and reflects the views and experience of a career spanning two continents: the first phase in Europe and the second in North America. It is not always easy to distinguish between effects due to changes in time from those caused by changes in geography, although that terrible word *globalization* has seriously undermined the influence of the latter. There may be many who find my analysis alarmist, and my proposed remedies unnecessary, or a sentimental desire to turn back the clock. I would be glad if this were so, for I love science with all my heart. But I recall a colleague who recently told me:

When I was young, I made a journey to Athens, Greece, to see where our civilization began. Many years later I made a journey across the Atlantic to Athens, Georgia, USA to see where our civilization had ended.

The longer I live, the more I have come to value those qualities that made Europe a great continent and reject those that made America a great country. I would gladly welcome a revival of the European spirit and traditions. It would make Science a better profession and the World a better place.

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