

THE KIRSCHNER ARTICLE AND HIV: SCIENTIFIC AND JOURNALISTIC (IR)RESPONSIBILITIES

by Serge Lang
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Part One

Editorial and scientific responsibility

In February 1996, the AMS *Notices* published a 12-page article "Using Mathematics to Understand HIV Immune Dynamics" by Denise Kirschner (pp. 191-202). This paper dealt with the mathematical modeling of HIV infection. Kirschner explicitly thanked "the editors for helpful comments and support in the writing of this article." For six years, I have been involved in gathering information about an extraordinary situation concerning HIV. I have a file more than an inch thick on the subject. The bottom line is that the hypothesis that HIV is a harmless virus is compatible with all the evidence I have studied; that purportedly scientific papers which I have followed up on HIV claiming otherwise are subject to very severe criticisms, pointing to severe faults; and that there is an ongoing phenomenon of mass misinformation, spread by NIH (especially in publications of the Centers for Disease Control - CDC), and spread in the scientific journals such as *Nature* and *Science* as well as in the press at large. I even published two articles on the subject in the *Yale Scientific* (Fall 1994, Winter 1995), reproduced updated in the Kluwer collection (see footnote 1) (and subsequently reproduced in my book *Challenges*, see below). I was therefore shocked to see the *Notices* spreading the orthodoxy uncritically.

In light of what I knew about the HIV situation, I immediately phoned Hugo Rossi, editor in chief of the *Notices*, and I sent him my HIV documentation. The documentation included:

- my *Yale Scientific* articles;
- articles by the mathematician Mark Craddock (School of Mathematics, University of New South Wales, Sydney, Australia), specifically directed at the use or misuse of mathematics in connection with HIV infection.¹

¹Mark Craddock, in the Kluwer collection *AIDS: Virus or Drug Induced?*, Peter H. Duesberg editor, Kluwer Academic Publishers, 1996:

"Some mathematical considerations on HIV and AIDS" pp. 89-95;

"A critical appraisal of the Vancouver men's study *Does it refute the drugs/AIDS hypothesis?* pp. 105-110;

- letters to and from government officials, such as Harold Jaffe, Director of the CDC;
- files containing critical analyses of published articles which received wide attention in the press (scientific and otherwise, including the *New York Times*).
- Subsequently these documents were complemented by my *Journalistic Suppression and Manipulation File* (1995-1996), and the File entitled: *Throwing Math and Statistics at People* (Summer 1997).

On the phone I suggested to Rossi that if the publication of Kirschner's article was to be taken seriously, it would involve the *Notices* in a morass for which the AMS was not equipped institutionally. To minimize the time wasted by everybody, I suggested to him that after he processed the documentation, he might write his own editorial statement to the effect that when he arranged for the publication of the Kirschner article, he did not know about the simmering controversy on HIV. Given the additional information, he could ask readers simply to disregard the published article, which readers were not in a position to evaluate without a substantial amount of additional material. Providing this material might result in an open-ended controversy in the *Notices*. Just for a start, the *Notices* might solicit an article by Mark Craddock analyzing the Kirschner article. Rossi answered me by mail without even waiting to receive the material, and he wrote that no matter what this material contained, he would not make a "Stalinesque confession" (his interpretation of what I was asking). I did not read his letter further, and I sent it to Cathleen Morawetz, president of the AMS, together with my resignation from the AMS, because I wanted no part of the responsibility as a member of the AMS to deal with the situation the editors had created with the publication of the Kirschner article, and with Rossi's subsequent position.

Public relations. There is some evidence that the Kirschner article was not even meant to be read, but was merely a public relations gesture using HIV combined with math to emphasize the importance of "relevance", "applications", and "social responsibility". Indeed, when the AMS President wrote me back, she suggested that I write a letter to the editors for publication, and she added: "I would recommend a short letter - it takes less time to write and is much more likely to be read - since limited time and space is a problem for us all." However, the very extensive space occupied by the 12 pages of the Kirschner article, written with the "helpful comments and support" of the editors, did not present a problem to them, nor apparently to the AMS president. Of course, I refused to engage in the superficial dealings the AMS president was suggesting. Barring a possibly short statement by the editor as I was requesting, what I saw as my responsibility as an AMS member would be to insure publication of an

"Science by Press Conference" pp. 127-130.

My articles are:

"HIV and AIDS: Have we been misled? Questions of scientific and journalistic responsibility" pp. 271-295;

"To fund or not to fund, that is the question: proposed experiments on the drug-AIDS hypothesis" pp. 297-307.

extensive documented evaluation of the type Mark Craddock provided in his articles. I was neither able nor did I have the time available to do it myself, but if the AMS higher ups were serious about informing the readership properly, they could have solicited Mark Craddock as I suggested.

The Landau editorial. Subsequently, in February 1997, the *Notices* published an editorial by Susan Landau (Associate Editor) entitled "Mathematicians and Social Responsibility". The editorial is presumptuous, and Landau subsequently evaded the very responsibilities she invoked in the big-time rhetoric of her editorial. Among other things, Landau asserts: "Our responsibilities extend to preparing the biology students for the work they will actually do (rather than giving them a standard calculus course with the odd population biology example thrown in)." First, I object to her put down of the "standard calculus course with the odd population biology example thrown in". The population biology example is not "odd". Principally, what does her admonition mean in the specific case of HIV and AIDS, in light of the criticisms which have been leveled at the orthodox line on HIV? I sent her my HIV file. What would the *Notices* do about the Kirschner article? What would she do? She wrote me on 12 September 1997: "For the last several months I have been receiving mail from you regarding HIV and AIDS. Despite being an Associate Editor of the *Notices*, I am not really following these issues, and I would like to be removed from your mailing list." So how do "our responsibilities" apply to her, especially since she is an Associate Editor of the *Notices* and the editors provided "helpful comments and support in the writing" of Kirschner's article? Despite having shared the responsibility to publish the Kirschner article, she claims that she is "not really following these issues" and she rejects information about them. Thus *de facto* she is evading her responsibilities in at least two respects: those invoked in her editorial, and those arising *ex officio* as an Associate Editor of the *Notices*. Some letters to the editor paid lip service to her editorial, e.g. in April and May 1997. The authors of these letters were apparently unaware of the HIV pathogeny controversy, the problems with the original Kirschner article, and the post-publication abdication of responsibility by the editors of the *Notices*. I shall return to questions about the Landau editorial at the end of Part Two.

A letter from Arthur Gottlieb, rethinking the problem. Certain events induced me to reconsider the importance of the Kirschner article, and to follow up more actively on the AMS involvement. On 16 May 1997, Arthur Gottlieb M.D., Chair of the Microbiology/Immunology Department at Tulane University, wrote me to ask for my professional opinion concerning the Craddock articles analyzing certain mathematical defects in published and famous articles on HIV/AIDS (see Part Two below, and especially footnotes 4 and 7). I had corresponded previously with Gottlieb, because he had heard of me through the grapevine, and had sent me a letter which he had written to the editors of the *New York Times*, but which was not published. Of course, I circulated his letter to my cc list. I strongly supported Craddock's analyses which concerned especially a "model" by Ho and Shaw, who are two famous HIV researchers. For example, a year ago, Ho was named TIME Man of the Year. Gottlieb wrote me:

I met Mark [Craddock] on a visit in Sydney last year and have been particularly interested in his views of the Ho/Shaw model of HIV pathogenesis which has now acquired the status of a law of nature in the AIDS-HIV community...

I think there is more than a matter of scientific debate here. My experience has been that when models of this type are presented to broad biological-medical audiences, the math is rarely critically analyzed -- most people are content with the declaration that a biostatistician has come up with the particular equations that are said to describe the situation. It is the rare individual, indeed, who would raise a meaningful question in such a context. The Ho/Shaw model is now a widely accepted paradigm for HIV pathogenesis. Moreover, it is being used as a basis for therapeutic guidelines in respect of HIV ("treat early and hard"). That, I think, is of concern, if indeed there are serious questions about the validity of the model. It would be good to have your views on this.

Two years ago, at the time of Kirschner's article, it did not seem to me worth while getting further involved setting up the AMS. However, since a person as solidly placed as Gottlieb in the medical establishment has now raised questions which involve joint responsibilities with mathematicians, I revised my estimate of the importance of dealing more thoroughly with an evaluation of various uses of "mathematics" in connection with HIV. I am now dealing with the AMS as an outsider, but the higher ups at the AMS had, and still have, the responsibility to follow up on Kirschner's article, and they have the responsibility to take into account articles such as those by Craddock, and other articles which are beginning to appear (cf. footnote 7 below). The evidence so far is that they won't do it without some outside intervention. For two years I have kept some higher ups in the AMS abreast of the situation and my HIV file, with no visible result. In particular, the *Notices* Staff Writer Allyn Jackson did not report the events surrounding my resignation, nor did she report the documentation which I provided on HIV.

My book *Challenges*. In November 1997, my book *Challenges* appeared, published by Springer Verlag. The book contains an extensive chapter (114 pages) on HIV. Beyond my two articles, the chapter is based on my various files on HIV. The existence of this book now makes it easier to disseminate information about HIV, and thus also contributed to my decision finally to write a piece for publication in the *Notices*. Readers will note that Dr. Gottlieb provided a one page statement at the end of the HIV chapter, p. 714, where he says about the controversy over HIV pathogeny:

...In this chapter, Prof. Serge Lang has well documented the basis of this controversy, and has provided a sobering picture for the reader of the polity of thinking that has characterized this field...Models of how HIV and cells of the immune system replicate, which have not yet sustained the rigor of thorough scientific discussion and critique at both the biological and mathematical level, are accepted as if they were laws of nature...

A review of the scenarios which Lang has painted should give the thoughtful reader pause as well as some insight into how doctrinaire thinking can develop and be perpetuated.

In a piece addressed to the *AMS Notices*, it is appropriate to go into certain technicalities. In a second part, I shall deal more specifically with mathematical aspect of the HIV problem, and the Kirschner article in particular. Be it noted that I sent my HIV file and various criticisms (by Craddock, Gottlieb, and me) to Kirschner in August 1997, but I have had no reply from her.

Part Two

Specific Mathematical Criticisms

Craddock's articles. I have distributed widely the Craddock article on Ho & Shaw's work: "HIV: Science by Press Conference" (cf. footnote 1). Craddock provides 3 pages of detailed documentation for his conclusion: "...this new work is about as convincing as a giraffe trying to sneak into a polar bears only picnic by wearing sunglasses (as Ben Elton might say)."² The mathematics Craddock analyzes here are at the level of freshman calculus. In the other article "Some mathematical considerations on HIV and AIDS", the level is even more elementary. Craddock writes in a very convincing way, by using unpretentious language and making his objections very specific about very concrete items. I have found his articles so well formulated that I have asked various scientists to take them into consideration, without success. To give an unqualified endorsement of Craddock I would have to read the original papers by Ho & Shaw, which I have not done, and am not really competent to do, lacking training in biology. But I don't need any further competence to recognize the legitimacy of Craddock's criticisms. His specific, documented criticisms include:

- Objections about the mathematical modeling and certain assumptions, not made explicit, and not justified by empirical evidence; unjustified assumptions unrelated to the empirical data.
- Questions about the meaning or significance of the data used by Ho and Shaw.
- Lack of control groups, in two contexts p. 129:
 - (a) "Neither group [Ho and Shaw] compared the rate of T4 cells generated in the HIV positive patients with HIV negative controls!"³
 - (b) "It must surely be admitted that the system they are trying to study, namely the interaction of HIV with T4 cells, might behave substantially differently in people

²The work under review is: Ho et al. *Nature* Vol. 373, 12 Jan 1995 pp. 123-126; and Wei et al. *ibid* pp. 117-122

³He goes on: "Both groups assert that in HIV infected individuals, up to 5% of the circulating T4 cells are replaced every 2 days. This information is hardly new, Peter Duesberg says something similar in a paper in the Proceedings of the National Academy of Sciences from 1989. Except he states that 5% of the bodies T cells will be replaced every 2 days, in healthy people."

who are not being pumped full of new drugs, in addition to 'antiretrovirals' like Zidovudine?"⁴

- Lack of warning that certain purportedly therapeutic drugs have toxic effects.
- Lack of justification for attributing the production (rather than destruction!) of T4 cells to HIV.⁵

Finally, Craddock points out that if one formulates the model correctly, then what it predicts is not the same as what Ho & Shaw say it predicts.⁶ His remarks are in line with the implausibility that it takes ten years for a virus with generation time of 1 to 2 days to achieve effects causing death.

The responsibility for confronting these criticisms lies with the authors he criticizes, and with the relevant scientific journals (such as *Nature*, *Science*, or *The Lancet*) for publishing both the criticisms and whatever replies the authors make. If they make none, scientific and journalistic standards require that readers of these journals be so informed. However, the scientific journals have actually failed in their responsibility. They have skewed and prejudiced scientific discourse, and obstructed the usual self-correcting mechanisms of science. For extensive documentation of these assertions, cf. my book *Challenges*.

I see no reason to deviate from the standards that scientific discourse take place openly in journals, and that the scientists whose works are questioned or criticized be held responsible for answering the questions and criticisms. In particular, it would be entirely appropriate for Ho and Shaw to be confronted directly with the Craddock criticisms, and for them to answer these criticisms, whether to acknowledge their validity, or to counter them if Ho & Shaw are able to do so. Barring specific justified

⁴This is similar to the reason Arthur Gottlieb wrote to me in his letter of 16 May 1997: "I might say that I have been skeptical of the validity of the Ho/Shaw model for several reasons, but principally because it is based on observations in subjects who were therapeutically perturbed by use of a protease inhibitor."

⁵As Craddock writes: "The logic here is remarkable. It is claimed that HIV sends the immune system into overdrive as measured by a supposedly accelerated production of T4 cells. Between 100 million and 2 billion are produced each day in the patients that were studied."

⁶As he writes: "When correctly formulated (Craddock, *Ibid*), what emerges is stunning. Ho et al.'s observations combined with their simple model for T cells and virus, predict that the T cell count should reach an equilibrium state quickly. Meaning exponentially fast...When you add terms to the equation to describe the effects of Virus (inexplicably, they do not include the effects of the virus on the T-cell population in their model. I thought HIV was supposed to be killing these cells somehow), then include the expression for the amount of virus that they give on p. 124, you get a picture of 'HIV disease' that bears no relation to what happens in actual patients. AIDS should develop in days or weeks. There is no possible way it can take ten years. This emerges from Ho et al's own model."

rebuttals to Craddock's specific criticisms, we are entitled to regard these criticisms as valid, and they invalidate the Ho and Shaw papers which Craddock analyzes.⁷

The *Notices* article by Denise Kirschner. The Kirschner article in the *Notices* is an echo of Ho and Shaw. The mathematics in her article are somewhat more involved than the mathematics in the Ho & Shaw articles (her differential equations are more complicated). I have not checked them. But even if correct, to what extent is her use of mathematics useful to understand whether HIV is pathogenic or not, and if so, how? I fully share Craddock's conception of science: "Science is about making observations and trying to fit them into a theoretical framework. Having the theoretical framework allows us to make predictions about phenomena that we can then test. HIV 'science' long ago set off on a different path." Kirschner asserts p. 195: "Clinical data are becoming more available, making it possible to get actual values (or orders of values) directly for the individual parameters in the model." So the paper itself does not contain "actual values". The way the paper is written does not fit the definition of science recalled above, and does not inspire my confidence. I shall give a few concrete reasons why not.

- Kirschner repeats one orthodox line (p. 191) that "HIV is the virus which causes AIDS (Acquired Immune Deficiency Syndrome)" without any acknowledgement that in

⁷(a) Some criticisms of the Ho and Shaw articles already appeared in letters to the editor in *Nature* (375, 18 May 1995). One of these letters, by Bukrinsky et al. (pp. 195-196) stated: "A definitive answer awaits accurate estimates of the turnover and half-life of both proliferating and peripheral CD4+ T cells in healthy individuals, normative data for which the immunological community strangely lacks a robust appraisal." In plain English, Bukrinsky et al. make the same point already mentioned, that no control groups were used to compare the behavior of CD4+ T-cells in individuals who are healthy, sick, HIV positive, or HIV negative, in various combinations. Ho and Shaw answered the Bukrinsky et al. comment quoted above as follows: "...we do not understand their logic of comparing our calculated CD4 lymphocyte turnover rates with previous estimates for normal peripheral blood mononuclear cells..." But the logic is clear to me. In plain English, the fact that turnover of T-cells is the same in Ho & Shaw's CD 4 lymphocytes as in previous estimates for peripheral blood as in mononuclear cells constitutes clear evidence that HIV is neither the cause of T-cell destruction, nor of harm to the immune system (which has been claimed). I wrote to Bukrinsky on 18 July 1997 to ask him to straighten me out if I misunderstood the situation. He did not answer my letter.

(b) Another letter by Ascher et al. (p. 196) stated: "...But the central paradox of AIDS pathogenesis remains...there is about 100-1,000-fold more cell death than can be accounted for by the observed rate of virus production⁵. It is a murder scene with far more bodies than bullets."

(c) There is a detailed critique of Wei et al. and Ho et al. in an article by Peter Duesberg and Harvey Bialy, "Responding to 'Duesberg and the new view of HIV'", Kluwer collection pp. 115-119.

(d) Further critiques of the mathematical analysis of Ho and Shaw (Wei et al.) have recently begun to appear. See Z. Grossman and R. Herberman, *Nature Medicine* Vol. 3 (1997) pp. 486-490; and G. Pantaleo, *ibid.* pp. 483-486. Cf. also the accompanying editorial: "Two commentaries challenge current thinking in HIV research and treatment."

the Centers for Disease Control list of 29 diseases defining AIDS in the presence of HIV, about 40% of these diseases do not involve immunodeficiency, and that a low T-cell count is only one of the 29 diseases. The assumption that "HIV causes AIDS" is made without justification and without reference to a scientific paper justifying this assumption. After six years of looking into the HIV pathogeny question, I have not learned of the existence of any such paper.

- She repeats the orthodox line (p. 193): "When HIV infects the body, its target is CD4⁺ T cells. Since CD4⁺ T cells play the key role in the immune response, this is cause for alarm and a key reason for HIV's devastating impact...Clearly, there is a necessity for treatment of HIV infection." Here she relies unquestioningly on the orthodox line, which I and a number of other scientists do not automatically accept. There is evidence going against all three assertions: CD4⁺ T cells being a target of HIV, a devastating impact being due to HIV, and the necessity for treatment of HIV infection. Aside from the point raised in footnote 7, what about T-cells which live in the presence of HIV? As some scientists including Peter Duesberg have pointed out, HIV is mass produced in immortal T-cells, both by scientists and drug companies. Her only qualification is: "The course of infection with HIV is not clear-cut. Clinicians are still arguing about what causes the eventual collapse of the immune system, resulting in death." However, barring further evidence to the contrary, the way she builds up her proposed model fits Craddock's characterization of "arcane speculations about molecular interactions".

- Several of Craddock's criticisms of the Ho & Shaw article are applicable to her article to the extent the following objections are valid. For example, she writes: "...it has been shown that infected CD4⁺ T cells live less than 1-2 days [10]; therefore, we choose the rate of loss of infected T-cells, μ_T , to be values between .5 and 1.0." How justified is this choice? Her reference [10] is not even an original scientific paper but is partly a laudatory review in *Science* of the Wei et al. and Ho et al. articles, editorializing about what is seen as their implications.⁸ Is her model a priori irrelevant because she did not take into account certain essential factors? For instance, she gives no evidence that she took control groups into account. The half life of T-cells for infected or uninfected people is apparently the same. (Cf. footnote 3.) How did she take into account the presence of drugs or, as Arthur Gottlieb has brought up, protease inhibitors? (Cf. footnote 4.) She does state: "To include AZT chemotherapy in the model, it is necessary to mimic the effects of the drug which serves to reduce viral infectivity..." But there is no evidence that she even considered possible toxic effects of AZT, and she only mentions a parameter which "is multiplied by a function which is 'off' outside the treatment period and 'on' during the treatment period." It's not clear that this kind of "model" represents what actually goes on. As far as I can tell, we are witnessing here a cumulative chain of defective science, uncritically invoking defective results by others, and propagating misinformation combined with an irrelevant mathematical formalism.

⁸Her reference [10] is to J. M. Coffin, "HIV populations dynamics in vivo: Implications for genetic variation, pathogenesis and therapy," *Science* **267** (1995) pp. 483-489.

- In addition, am I reading correctly that the Kirschner model is in direct contradiction with the Ho & Shaw model, and also with empirical evidence for production rather than destruction of T-cells? Indeed, as we have recalled above, the Ho & Shaw model leads to "accelerated production of T4 cells", and an exponential approach to equilibrium. (Cf. footnotes 5 and 6.) So what's going on?

Funding. I note that the NSF supported Kirschner's work. As far as I am concerned, publication of her article in the *Notices* came at a time when money is more than tight for mathematics. Higher ups in the AMS including editors of journals want to make "mathematics" appear relevant to society at large, so that mathematicians get more support from the government. But invoking relevance is not a license for funding and disseminating uncritically certain points of view reinforcing the orthodoxy. To the extent that substantial criticisms of the Kirschner article are valid, including the possibility that it is worthless even as an "arcane speculation", the NSF funding of the 12-page Kirschner article is questionable; and its uncritical publication by the AMS, giving a mathematical aura to HIV and an applied aura to mathematics, is journalistically and scientifically irresponsible without a critical follow up, which the editors or AMS higher ups so far have refused to provide.

Math and Medicine. I see no evidence that her paper fits her conclusion p. 201: "Through this simple example, I hope it is also clear that there can and should be a role for mathematics in medicine." Even though her paper might be defective, I am not questioning the big time generality whether there is a role for mathematics in medicine. However, it is NOT clear to me that her paper is a positive contribution to medicine. This remains to be seen, after competent persons (including Craddock and Gottlieb) have scrutinized it. Furthermore, so far, the "model" she proposes is disjoint from experimental testing or evidence, and from medicine. It is just presented as an independent entity, and I don't see any indication how it might be used clinically, although she writes: "Now that we have a model that we believe mimics a clinical picture, we can use the model to incorporate treatment strategies." Thus she substitutes beliefs ("we believe") for scientific experimental verification. The conclusions she draws are only based on the theoretical model, not actual practice on patients, and her model is biased in favor of the orthodox view. I hope someone such as Craddock or Gottlieb will be willing to give a more extensive analysis, which I am not able to give at the moment.

In summer 1997 I sent a copy of Kirschner's article to Arthur Gottlieb, and he answered: "I have put the Kirschner article on my list of things to do and will read it with a critical eye. cursory review of same indicates no reference to functional CD4+ cells as a parameter to be considered. That is probably a fatal flaw, as every CD4+ cell is not equal to every other CD4+ cell." However, he also wrote me that he would be very busy with his course last fall, and I have not heard from him since the end of last summer.

Kirschner also states: "The biggest obstacle facing collaboration is the inability of clinicians to understand advanced mathematics, and, on the mathematician's part, the

lack of knowledge of the underlying medical problem." With such a sentence, she bypasses the problems raised by Mark Craddock's criticisms of the Ho & Shaw articles, and the problems which exist with her own article as listed above, as well as the problems with her references. Obstacles to collaboration are not totally ordered, and there may not be a biggest one; but as far as I am concerned, a big obstacle facing collaboration is that criticisms of existing articles are ignored by authors, ignored by editors such as those of the *AMS Notices*, and suppressed by journals such as *Nature*, *Science*, and the *Lancet*. Cf. for instance the exchange between Duesberg and *Nature* editor John Maddox in the Kluwer collection, pp. 111-125. For further documentation, cf. my book *Challenges*.

The existence of various articles on mathematical modeling, especially in connection with HIV, raises further questions about the use of mathematical modeling in biology generally. To what extent has such modeling been used scientifically, resp. medically? To what extent has it just amounted to throwing mathematics and statistics at people, thereby producing "mystification and intimidation" (as Koblitz once characterized this activity by some practitioners of some political science), but making no genuine scientific or medical contribution?

Da Capo

Returning to the issue of responsibility raised in Susan Landau's editorial: when mathematicians teach calculus, or biologists teach the use of mathematical modeling, to what extent do teachers warn students about passing off "mathematical modeling" as science, when a purported "model" is not based on empirical data, and is proposed (let alone accepted) quite independently of empirical verification? How does one document the warnings? Both the Ho & Shaw and Kirschner articles are based on assumptions which are not rooted in empirical evidence. Does one include a warning about making such assumptions explicit when teaching calculus and biology? What are the implications of holding up resp. not holding up in the classroom the Ho & Shaw and Kirschner articles as models of so-called mathematical modeling not justified by empirical conditions? *De facto* can we, do we, shall we engage a calculus class in a discussion of the Ho & Shaw and Kirschner articles (among others), bringing up documentation to the attention of the class to justify the criticisms I and others have made? What would happen if we did so? The social, academic and practical forces against doing so are multiple, and obviously very strong. For an even broader context in which such questions can be raised, including the context of social sciences, cf. my book *Challenges*.