The written questions, and the answers thereto (17 March '11)

Bauer, Melissa

Q: Given your frustrations with the academic environment, what other settings have you found helpful in reaching your level of expertise?

A: There haven't been other "settings" bearing on my academic self-development. Essential has been *extensive reading* together with *critical reflection* – following F. Bacon's counsel: 'Read not to contradict, nor to believe, but to weigh and consider.' For much too long I generally believed and, thus, remained in many ways badly misguided.

Brunet, Laurence

Q: [Q to be produced.]

Cohen, Jacqueline

Q: What is the process by which evidence is transformed into knowledge?

A: This important but generally neglected question is addressed rather extensively in the text 'Up from clinical epidemiology & EBM' (q.v.).

Fortin, Elise

Q1: How can we generate epidemiological knowledge without basing ourselves on evidence?

A1: Much of medical knowledge, epidemiological knowledge included, has preceded medical science. All of epidemiological science is empirical (rather than theoretical) science, thereby with a *critical role for evidence* (together with reasoning). Cohen, above, asks about the process by which evidence is – or could be – translated into knowledge.

Q2: In our "Causal Inference" course it became obvious that study results are usually biased and unreliable. Is there a way out of [this, leading to reliable knowledge]?

A2: There is a way, to quite an extent, through *needed major improvements* in two areas: (1) epidemiological research and (2) journals (epid'c and other) publishing reports of it. I address these matters extensively in the 'Up from …' text. But in the end, all of scientific knowledge is liable to be erroneous, and the responsibility of each scientist is to help minimize this (in the production of evidence and in the translation of the evidence into knowledge).

Gariépy, Geneviève

Q: [Q to be produced.]

Gough, Ethan

Q: External validity is often given less importance than internal validity in epidemiological research. Why is this so? When is the opposite [to be the case]?

A: I don't master the psychogenesis of that differential valuation except for the obvious: it is natural and correct to take internal validity to be a sine qua non for external validity, of the more proximal concern in this sense. But: internal validity (in reference to the study base, possibly biased) is worthless in the absence of external validity (in reference to the domain – abstract – of the object of study). Needed is a study base free of selection bias and valid documentation of the experience in the study base (conditionally on all confounders in an etiogenetic study). The purported duality in validity is not a very natural one in this.

Hajna, Samantha

Q: [Given that textbooks address methods] without having the 'end' in sight, … how can this be rectified? … how the authors should improve on this?

A: The authors should come to appreciate that the object of study – implicit in the form of the study result – does not have its existence a priori; that it needs to be designed, just as the methodology does. So, the *textbooks should address epidemiological studies' object design* and not only their methods design. I address object design in the two course texts. By the way, I just learned that this 'seminar' series is, specifically and solely, about (advanced) 'methods (*sic*) in epidemiology'!

Magalhaes, Sandra

Q: Given … that we are to seek simplicity in science (our [objects of study]), how do 'we' incorporate all the complexity (DAGs, interacting types, non-identifiability) in our quest for evidence [toward] knowledge?

A: What you list as examples of complexity are not features of the object of study. Insofar as one is to take seriously these recent themes in the theory of epidemiological research, they have bearing on the development of a study's object design and methods design, not the nature of these (as novel complexities in them).

Motid, Layla

Q: Can you please explain why the rare disease assumption is not relevant?

A: I can and will: Consider a study base with index and reference rates c_1/B_1 and c_0/B_0, respectively, and the researchers' concern to document the rate ratio, $(c_1/B_1)/(c_0/B_0)$. The etiogenetic study involves a case series of size $c = c_1 + c_0$ and a base series of some size $b = b_1 + b_0$, where b_1 and b_0 are stochastically proportional to B_1 and B_0, respectively. The empirical RR, corresponding to $(c_1/c_0)/(B_1/B_0)$, from such a study is $(c_1/c_0)/(b_1/b_0)$ – with no 'rare disease' assumption involved in this. (OSM, '76, which you studied earlier in this 'seminar.')

Moqueet, Nasheed

Q: Are there medically … relevant questions that [epidemiological or meta-epidemiological clinical] research is ill-equipped or not equipped to answer?

A: It is necessary to understand that such research practically never 'answers questions' but, instead, merely provides evidence about objects of study (about the magnitudes of the parameters in these). Now, the research can address phenomena of illness (the rates/probabilities of their occurrence in defined domains, incl. as to subjective phenomena), but *it cannot meaningfully address the disutilities* – subjective valuations – associated with these (having to do with quality and/or quantity of life). This is a very major limitation, *not understood* by advocates – initially within the National Institutes of Health of the U.S. – of studies on interventions' (incl. diagnostics'!) effects on 'quality-adjusted life years.'

Rushani, Dinela

Q1: Agent vs. cause

A1: Implicitly, the question seems to be whether an/the agent involved in an illness can be viewed as a cause of the illness. As I explain in the texts, the common affirmative answer to this question has reflected a *major misunderstanding* in medicine. Once tissue presence of M. tuberculosis got to be definitional to tuberculosis (per R. Koch), the agent (its tissue presence) no longer was an antecedent to the illness; it no longer could rationally be thought of as being causal to the illness. Ditto for silicosis, etc. The *proximal cause* – universal, necessary – of tuberculosis (as it is now defined) is effective exposure to the agent together with susceptibility to this, as I explain in the texts.

Q2: Can *absence* of something be cause of something else?

A2: Yes it can. Absence of X is presence of non-X, diet's deficiency in a micronutrient (X), say.

Smith, Leah

Q: Is [it] your goal to make epidemiologic[al] evidence … completely objective? Or [are] there always elements of 'art' [in the evidence]?

A: Evidence is (completely) *objective by definition* – that is, agreed upon by all qualified consumers of it (hypothetical ones included). In the *production* of the evidence in any given study (original or derivative) there is, unavoidably, a lot of scope for 'art.' An eminent example of this has been the choice between primary and secondary definition of the source population in an etiogenetic study – although suitably principled design of the identification of a primary case series makes the secondarily-defined source population to coincide with one having primary definition.

Sohn, Hojoon

Q: What is the role of inter-disciplinary research in epidemiology [i.e. in epidemiological research]?

A: There is a need to distinguish between *two meanings* of 'inter-disciplinary.' A given study can be said to have this quality if it draws from 'multiple' disciplines in the design of is object and/or its methodology, even in the absence of involvement of representatives of those disciplines in the team of investigators; but in a different – the common – meaning a study is inter-disciplinary – or multi-disciplinary – if the team of investigators is constituted by representatives of 'multiple' (several) disciplines. Mastery of 'multiple' disciplines – in relevant regards – is *generally required* in epidemiological studies, but this does not mean that separate representatives of these disciplines necessarily are needed. *The Principal Investigator needs to master all that is relevant* to the study, whether with or without the involvement of separate representatives of each 'multiple' discipline in the research team.

Sun, Zhuoku

Q: [To what extent could epidemiological research produce the scientific knowledge-base for clinical medicine, for the practice of this]?

A: The relevant research is not epidemiological; it is *meta-epidemiological*, quintessentially 'applied' research for clinical medicine (addressing gnostic probabilities through the study of rates). The knowledge-base should be understood to bear on gnosis only, not on decisions by the clinician (the proper decision-maker being the client). The relevant research addresses gnostic probability functions; and while this research has barely begun, *it can produce the evidence for the entire knowledge-base* relevant to a given discipline of clinical medicine – for

incorporation in discipline-specific expert systems (for each of the three genera of gnosis). The urgent need is to develop the GPFs as a matter of harvesting experts' tacit knowledge in that form, for incorporation in practice-guiding expert systems. The scientific counterpart of this quasi-scientific knowledge base for clinical medicine will be much slower in its development. See 'Up from …'

van Gaalen, Rolina

Q: [Q to be produced.]

Hanley, James

Q: Could you give us a concrete example from epidemiology or from physics or psychology, or whatever you choose, of an "object of study"?

A: I think I could. To wit, I'll try to give a few.

1. Arguably the most brilliant and most consequential experiment of all time has been the testing, by Mickelson and Morley, of Maxwell's idea that the waves of electromagnetism are propagated in ubiquitous 'ether.' Their *proximal concern* was to study the very existence/non-existence (formal object) of this 'ether' (material object). To this end, they *designed the object of study secondarily* to be the speed of light relative to an Earth-bound observer, as this depends on the direction of the light ray's motion relative to that of the Earth's motion in space (à la Doppler effect). And to study this, *they designed the ultimate object of study* to be interference of two light beams – the occurrence/non-occurrence of this – as they have left in a single pencil of light, have been made to diverge at a straight angle, and then have been made to converge again (in a system of mirrors). (The design of the methods of this study – most elegant – was entirely subordinate to this design – ingenious – of the object of the study, the result on it – negative: no interference – being fundamental to Einstein's special theory of relativity.)

2. For a study on the *etiogenesis of an illness*, as explained in the 'Up from …' text, the object of study generally is an incidence-density ratio, IDR, for a particular illness in a particular domain; and the particulars of this should be the result of thoughtful design of the object of study. The investigators should *design a presumedly tenable model for the ID*, generally a log-linear one. If at issue is etiogenetic hypothesis testing, the model would generally involve a single term for the determinant contrast(s), and it would involve thorough representation of all of the ID's extraneous determinants that could remain as potential confounders (so as to make the relation to the determinant at issue conditional on all potential confounders). If, however, at issue is quantification of the IDR (upon the hypothesis having been generally accepted), product terms allowing for modification of the IDR by the potential confounders (i.a.) generally need to be added into the model. The model is to be designed in two stages, first conceptually and then in

operational terms. For example, is the concept of case to be operationalized as any rule-in diagnosed case occurring in the study base, or is it to be defined as being typical and severe (for validity assurance)? The designed model for ID implies the corresponding model – confounder-conditional – for the IDR to be studied; and if *implies the logistic model to be fitted to the data* (upon their translation into the statistical variates involved in the model) – this in addition to the particulars of the study design in the framework of the generally singular structure that logic dictates for an etiogenetic study (instead of the 'cohort' and 'case-control' structures; cf. the two texts).

3. In *clinical trials,* with data collection – but not object of study – designed by clinicians, statisticians 'analyze' (synthesize) the data; and the result of this now generally is a 'hazard ratio' (empirical value for incidence-density ratio) derived by means of Cox regression. But: designed ab initio should be a model for prospective (as of randomization) *incidence density as a function* of prospective time, choice of (prospective) intervention, and prognostic indicators (at prognostic T_0). This object of direct study implies, secondarily, what really matters: the corresponding *prognostic probability function*. (The empirical ID function is derived by means of a special – etiologic-study-inspired – variant of logistic regression, à la OSM, EJE 2010; 25: 671-5; cf. 'Up from …').

4. Epidemiologists in their studies on *screening for a cancer* generally take the object of study to be the 'effectiveness' of 'the test' (the initial diagnostic test, applied in community settings) in *reducing mortality* from the cancer (in a community); and the conceptualization of this as the 'effectiveness' as the object of study is evident in the general form of their study result: in a clinical (*sic*) trial, the extent to which the cause-specific cumulative mortality is lower in the screening (test) arm of the trial – from trial entry to the end of an arbitrary duration of follow-up, with an arbitrary (generally quite small) number of rounds of the testing, each test result left unspecified as to what further diagnostics, if any, are to follow, and each diagnosis (rule-in) left unspecified as to what treatment is to follow (these being treated as matters in the clinical 'black box'). *Results of this form – and thus the objects of study implied by them – are quantitatively meaningless*. For meaningful objects design for studies on screening for a cancer, see the 'Up from …' text. In brief, though, the central object – in reference to an expressly defined regimen of diagnostics and early treatment – should be understood to be the screening-associated *gain in the rate of the cancer's curability*, relative to no screening. See 'Up from …'

5. Epidemiologists – very high-profile teams of them – in their studies on aspirin use in febrile illness in childhood, this use in the *etiogenesis of Reye's syndrome*, were invariably left with the problem of uncontrollable confounding by the level of fever (aspirin being an antipyretic). They should have designed the *determinant contrast* to be that between aspirin use and, say, acetaminophen (Tylenol) use, instead of aspirin use vs. no aspirin use. With this design of the operational contrast (with acetaminophen in the role of a 'placebo'), *the object design would have been tantamount to prevention of confounding* by the level of fever.

6. ‘Clinical epidemiologists,’ following the lead from the National Cancer Institute of the U.S., have engaged in major programs of studying the ‘effectiveness’ of various types of imaging for the diagnosis of cancer, as though these tests were interventions and had health effects, and on several levels; and the methodology in these studies has been, accordingly, one of randomized trials. The profound wrongheadedness of this conception of the essence of diagnostics (as distinct from that of interventions) has led to *meaningless objects in research on diagnostics*. This problem is addressed quite extensively in both of the texts made available for this ‘seminar.’

7. Central in the interests, and objects of study, of ‘clinical epidemiologists’ have been *diagnostic tests* (other than screening tests); and in respect to a particular test, the principal objects of study about it have been its *‘sensitivity’* and *‘specificity’* for the diagnosis about a particular illness – these in reference to some arbitrary cut-off points separating the test’s ‘positive’ results from ‘negative’ ones. Even the existence of these as (single-valued) parameters is a sheer phantasm, to say nothing about their relevance for diagnosis. In proper design of the objects for studies to advance the knowledge-base of scientific diagnosis, the first-order concern always is with *diagnostic probability functions*, including ones with test result(s) among the diagnostic indicators; and different additional functions pertain to the knowledge-base for the invocation of a (set of) test(s). See ‘Up from…’