Coggs-Scheidt

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January 9, 1981

Stephen Scheidt, M.D.
Senior Editor
Cardiovascular Reviews & Reports
525 East 68th Street
New York, N.Y. 10021

Dear Dr. Scheidt:

This is in response to the letter by Neurath and your November 18 letter.

I am grateful for Dr. Neurath's observations and take pleasure in replying to this distinguished and experienced clinician.

Neurath: "Coronary Artery Disease is a ubiquitous, very old disease. It has been found in well preserved Egyptian mummies and it is found today everywhere in larger and smaller numbers."

Blackburn: "My paleopathologist colleagues indicate that coronary arteries have never been studied adequately or systematically in Egyptian mummies. The finding of calcified plaques fallen and scattered in the pelvic basin, and lesions in rehydrated portions of abdominal aorta, suggest indeed that atherosclerosis was occasionally exhibited in these singly favored classes of Egypt. Such observations, of course, have little relevance to the systematic demonstration of large population differences in atherosclerosis and in manifest coronary disease, as carried out by trained pathologists, clinicians and epidemiologists (International Geopathological Study of the Tulane group, and Seven Countries Study of the Minnesota group)."

Neurath: "The least affected people are the East African Masai, who eat almost exclusively animal fat."

Blackburn: "It is remarkable that Dr. Neurath would give credence to the unsystematic, anthropological and anecdotal observations of an isolated, primitive herding economy in East Africa consisting of a few hundred adults, of unknown age, in the same light as the many thousands of men and women systematically studied in stable Western populations. The epidemiological evidence in the cultural isolates of Africa and the Eskimo

Blackburn: (cont'd) are unsystematic, and though they have lessons for us, they in no way compare with systematic evidence in the rural and affluent West."

Neurath: "But the erroneous interpretations to statistical figures stem from the fact that up to fairly recently this disease was called by a number of names . . . ."

Blackburn: "Dr. Neurath ignores the bulk of the CAD incidence data in my presentations which are derived from systematic clinical-epidemiological studies carried out by centrally trained teams with quality control field operations, centrally blinded coding of coronary events and standard measurement of physiological variables. These clearly show ten-fold differences in incidence of 'hard' CHD events, and the important relationship to the 'major' risk factors. With respect to changes in vital statistics about causes of death in the United States, it is not possible to explain by any fad in diagnosis or changes in international classification the remarkable rise of coronary heart disease deaths in the 1950s and 1960s in the United States, and the remarkable decline since the late 1960s. I think that, if Dr. Neurath would read carefully, he would find that my statements about these are modest, and that these death rate changes are simply compatible with a hypothesis about changes in risk characteristics, and the death rate lowering is probably real, not artifactual, and nothing more. It is the <u>congruence</u> of evidence which is important."

Neurath: "But population migrations occurred after World War II with more people settling in California, and the age distribution may also have played a part."

Blackburn: "This is a common interpretative error by clinicians unused to dealing with population data. Epidemiologists use only age-specific, not crude disease rates, in their assessments. Thus, their results are independent of changes in age composition of a population."

Neurath: ". . . It has been shown that ingestion of various amounts of eggs in the large number of young or middle-aged males show no change in serum cholesterol . . . . "

Blackburn: "The studies cited are selected among many more carefully controlled, isocaloric, metabolic ward studies over a wider range of diet cholesterol intake, which show an independent cholesterol raising effect of egg yolk. The studies he quotes

Blackburn: (cont'd) involve the addition of eggs to an already high cholesterol diet. They fail to control dietary composition otherwise as metabolic ward-controlled studies of diet composition."

Neurath: "Many cases of angina, myocardial necrosis and sudden death show no involvement of coronary arteries at all."

Blackburn: "It would be nice to see Dr. Neurath's documentation of this remarkable statement that is contrary to that of all clinicians and pathologists experienced in the field. Does he mean no atherosclerosis or no apparent thrombosis?"

Neurath: "The answer to the problem of CAD lies or will be given by basic research in biochemistry, biophysics and perhaps genetics."

Blackburn: "I suggest the answers, if there are answers, will not be given by basic research alone but by congruence of evidence from all medical research methods: clinical-pathological, laboratory-experimental, and population-epidemiological. Each contributes information complementary to the other. All are necessary for the broadest understanding of the causes and prevention of disease. Most of the major epidemics of civilization have been solved by this broader understanding. A few have been solved by an understanding of basic mechanisms alone. More have been solved by an understanding of the social-cultural influences in mass epidemic disease even before the detailed mechanisms were elaborated."

Neurath: "The declaration of CAD as a disease of aging, has shown further confirmation by the fortunately few incidents of progeria . . . ."

Blackburn: "It is unfortunate indeed if Dr. Neurath believes, despite the wealth of evidence in other cultures than our own, that atherosclerosis, coronary disease and stroke are natural accompaniments of aging. Perhaps it is too bad that he did not join his distinguished colleagues, who in the 1940s to the 1960s, in peripatetic ward rounds, and around the world in the 1960s and 1970s, nailed down the fact that many cultures have little or no manifest coronary disease."

Neurath: "The medical profession, but also organizations like the American Heart Association, have to stop preaching alleged ways of improving public health such as diets, exercise and so forth, which show no effect on the course of coronary artery disease and cannot even be properly assessed."

Blackburn: "We anxiously await, as we have for many decades, Dr. Neurath's, or others, Magic Bullet. Meanwhile, the congruence of clinical, experimental, and population data provide strong evidence that there are more healthy ways of living than the Western affluent pattern of eating, sedentary living and cigarette smoking. It is disappointing to hear a distinguished clinican argue against good hygiene, espoused by the notable medical philosophers and distinguished medical scientists of past and recent times."

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:jml

corres - Spodick

SAINT VINCENT HOSPITAL
Worcester, Mass. 01604

CARDIOLOGY DIVISION

David H. Spodick, M.D., Director
Professor of Medicine

University of Massachusetts
Medical School

May 8, 1981

Henry Blackburn, M.D.
Director, Lab. of Physiologic Hygiene
Stadium Gate 27
University of Minnesota
Minneapolis, Minn. 55455

Dear Henry:

I enjoyed reading your reply to the letter by Otto Neurath in Cardiovascular Reviews and Reports. Its content really puts his views in their proper place. Its form is a model for dissecting (citation by citation) ill founded criticism.

Somewhere I missed the work on the independent cholesterol raising effect of eggyolk that you mention. Could you send me the reference? If it is your own work, kindly send a reprint.

With best regards.

Yours sincerely, L.B.

David H. Spodick, M.D.

DHS/med

Send pc Keys, A.
Bias + misrepresentation invited. Ref. in my Levy ms.
5-1981 sent reprint #802 LB

Corrs - Spodick

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CARDIOLOGY DIVISION

David H. Spodick, M.D., Director
Professor of Medicine

University of Massachusetts
Medical School

Send Dr. Spodick 1980 LP reprint list + Levy optimal lipid reprints + file this

Henry Blackburn, M.D.
Director, Lab. of Physiological Hygiene
Stadium Gate 27
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Minneapolis, Minn. 55455

February 4, 1981

Dear Henry:

I am taking the liberty of enclosing a draft of my (protagonist) side of a debate "Medical and Surgical Therapy Should be Routinely Evaluated by Prospective Randomized Clinical Trials" at the ACC next month. You should recognize some of your own stuff here. I hope you could look ot over and make suggestions for changes. I feel particularly weak about discussing the alternative trial methods because of my sketchy statistical background.

Could you let me have any comments in 10 days?

With thanks and best regards,

Yours sincerely,

David

David H. Spodick, M.D.

DHS/med
Encl. 1

Send them list. Reprint list. optimal lipid? updated?

CORRES - SPODICK

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March 9, 1981

David H. Spodick, M.D.
St. Vincent Hospital
Worcester, MA. 01604

Dear David:

I have just come back from several weeks of travel and have belatedly gotten to your February 4th request. I am terribly sorry to have been unresponsive. I am delighted that you are involved in this debate, though I don't have the program in front of me to see who your antagonist is. May I make just a few general comments and then a few specific ones.

First, I think the production is characteristically informed, forceful, effective, honest, and forthright. Second, I think there should be a little sharper breakdown of subsections with pauses to summarize and sort of "put it away" for each argument. Finally, you will require a summary. A verbal debate versus a written article versus one for publication, of course, are all somewhat different in style and form, and some of your emotionally charged and more vivid language and adjectives may be appropriate to the oral debate situation, and perhaps best edited for the publication, if there is to be one. Some of the terms and analogies are, however, superb, such as "multiplication of anecdotes," "anecdotal data," "beguiling numerators," and "the battle of wits between unarmed opponents."

Your powerful opening criticizing the high volume bypass centers and their picking away at the VA trial is appropriate and a strong point. It is the responsibility of these centers to test well and early. It is their challenge and obligation as well as their opportunity.

The ethical case is particularly well-written and strong, and your five behavioral deterrents are choice.

I wonder whether you might not want to defuse the situation of the improperly done Anturome trial? That trial illustrates the danger of short cut design philosophies and drug company control of diagnosis, classification of end-points, analyses, and publications. The whole machination of that situation was complex and tragic, utilizing the enthusiasm of Sol Sherry, the over-whelming reputation of Braunwald, the submission of distinguished editors to lead article placement, the mysterious deaths of the two drug company analysts in short order following the FDA decision, and the unsupported battle of a

couple of serious and skilled but low level NIH employees to challenge the trial. All these are things that need to be in the back of your mind and defused with a short sentence or so about the possibility to do randomized, clinical trials improperly.

I also think that your argument of editorial responsibility in publishing bad trials is a powerful one which you must keep wielding. Editors in all clinical journals must have clinical trial expertise on their staffs or editorial boards.

On page 2, last paragraph, "obtaining a true answer" might better be "for approaching the truth about the benefit and cost of the new therapy." You might want to define the RCT there in such a way as to show that the patients are as comparable as possible, and that any given individual has an equal chance of being assigned to one versus another therapy. You have done well to point out that the trial doesn't even concern itself with mechanisms.

It would seem to me that it would be very powerful and hard-hitting to run down a very rapid list of what we have learned from trials, both in terms of positive effects, absence of effects, and negative effects. Such realizations might have fully as much weight as the sum of your powerful, theoretical arguments.

It might be helpful to throw in little definitions or descriptions in areas where the practitioner is usually not informed, such as at the bottom of page three when you speak of stratification (when appropriate); you might give a little brief salvo of where it is appropriate on the few variables that are normally strongly related - and indicate that stratification usually strengthens and improves the randomization process.

Somewhere here there should be stated very concisely the criteria of the scientific community for the conduct of a major clinical trial, so you can make your very convincing, older arguments that the earlier the better, and randomization from the first case may allow a much more rapid and efficient solution.

I very much like your listing of the five kinds of bias, and wonder if they are yours or others. I have not seen them listed with those particular terms. I wonder if "prognosis bias" would not better be "selective" or "severity" bias in which prognosis is different. In the area of observation bias, separate analyses for endpoints affected and unaffected by frequency of patient contact can be looked at to reduce that risk. Your discussion of the behavioral section is a superb analysis of fadism. Too bad to see old Benjamin Rush roasted again when he had so many great insights, particularly that mass diseases were intimately linked with social and economic change. But it is an awfully good example.

You may want to reconsider the example about gastric freezing when there may be a half a dozen others equally good. We just laid Owen Wangensteen to rest a couple of weeks ago, and his wife, Sally, and many of his devoted colleagues all over the country might be offended by choosing this particular time to illustrate his folly in this case. I admit it is a superb example and am simply suggesting that if you use it you might want to say a kind word about his leadership, his recognition, and his admission of this as a big mistake.

Your five deterrents to instituting trials is superb.

I think you handled the ethical situation beautifully. You will find another argument or two in the Ethics Committee deliberation about clinical trials in Circulation (52: September, 1975, AHA Committee Section, 5-9).

I guess I don't know what "optimizing informed consent" is.

On page 11, the interval data checking is usually done by a data monitoring committee whose function is separate from an advisory committee or at least is a subcommittee function.

I question your statement about stopping the trial at the "first sign." There should be careful design criteria for trial stopping, but the issue of specific quantitative prior criteria for stopping is still debated. That paragraph also suggests that all trials are designed sequentially. Most good trials have fixed numbers for their computed significance and power. The last sentence is a little confusing in that paragraph, "it is equally unethical to use too few patients," and so forth. The number of patients and the statistical methods are an integral part of the design and planning, and I am not quite sure what you mean about appropriate statistical methods "will be available." The statistical methods are well worked out beforehand in the trial design.

It would be useful to have a running staccato list of the alternatives and to tick them off one by one, rather than in the free-flowing narrative style you have used here. You have such a wealth of good points that they should all be in listed form as your behavioral characteristics, etc.

I think your point of randomization versus matching is a powerful one, and your criticism of the data banks along with the current reference to Katherine Detre's work is very important and topical. You might want to be conciliatory that when such approaches as registers and data banks provide the ideas for, and the impetus to, well-designed trials, and when they improve the quality of clinical information and data collection, that these are appropriate structures.

Is the term "adaptative methods" on page 13 yours? The paragraph and the technique are not as clear as could be. The life table and actuarial approaches are not "flawed as valued methods" for analysis of survival in trials with

unequal follow-up time, etc., etc. I wouldn't flaw the methods, I would flaw their use in replacement of trials. Your statement could be stronger that the usual projection of new treatment survivals do not necessarily encompass comparable populations, in fact, they usually don't encompass them.

Your paragraph on sequential acquisition of patients may not be entirely clear unless you add "with alternate assignments." At least I don't know what it means without such an addition. Your statement should not reflect on "sequential analysis" or "sequential design" of trials which contain in themselves adequate statistical safeguards. Sequential analysis is a biometric analytical term and model which should not be confused with what I take your use of the term here. It is used in randomized, clinical trial design as you know well. I am sure you don't want to get into a theoretical discussion of different trial designs. The invalid technique you describe in that last paragraph on page 13 should not then be confused with the valid sequential design or use of sequential analysis.

With regard to arguments against randomization, it may fail to sort the known as well as the unknown variables. Adequate sample size and stratification reduces this likelihood, and there are also some accepted, corrected measures for bad luck.

I don't quite understand line 8 "the statistical methods have been inadequate to show baseline differences."

Your replies to the issues of surgical experience and physiological soundness are excellent. Not only is a rising dose design, but an individual variable dose design, as compatible with a randomized, clinical trial. But they are both complicated, and thus, not clean.

I think your argument should end with a rapid fire summary of the accepted indications for a clinical trial and the statement that there is no more powerful and no more ethical approach available to science than the randomized, controlled trial. Finally, you may not have answered one of the primary criticisms of trials, that is their cost. This is readily done by comparison of the cost of the trials to the cost of trial and error, and the burden to society of untested and widespread therapeutic procedures.

I hope to be there.

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:jml

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CARDIOLOGY DIVISION

David H. Spodick, M.D., Director
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Copy.

March 11, 1980

Dear Henry -

Just got your superb analysis of my draft manuscript. I don't know how to thank you for your time and effort. I already modified it considerably but you have singled out many weak and muddled areas (as you may guess I do not have great depth in this subject). After doing the MS I learned that I have 12 minutes for the oral presentation. The result, as you may imagine is the truncated. My opponent, Kahn-Tuna is a top man and we should be far from 180° apart.

Looking forward to thanking you in person!

Regards,

Alan