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A conversation with Paul Meier

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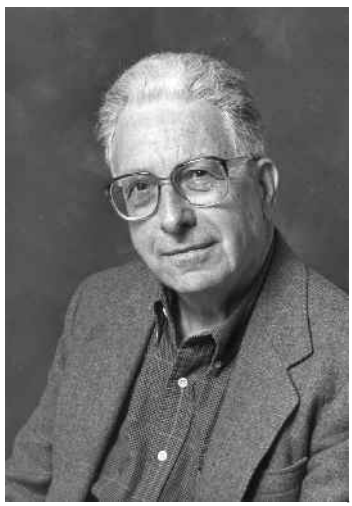

Meier shortly after joining the Mailman School of Public Health, Columbia University (1993).

Paul Meier in a lunchtime discussion with colleagues, Stanford University (1982).

Introduction

A 1951 graduate of Princeton University, Paul Meier (b. 1924) belongs to the first generation of statisticians to enter medical research after the second world war. He taught in the Department of Biostatistics at The Johns Hopkins University from 1952 to 1957, when he joined the Statistics Department at the University of Chicago. In 1992, he moved to the Mailman School of Public Health, Columbia University, where he is Howard Levene Professor of Statistics. A fellow of the American Association for the Advancement of Science, the American Statistical Association and the Institute of Mathematical Statistics, Meier has served as president of both IMS and the Society for Clinical Trials.

Best known to methodologists for the development of the Kaplan–Meier estimator, Meier had a long career conducting, overseeing and commenting on clinical trials [1]. His involvement began with the 1954 Salk polio vaccine field trials and their aftermath [2,3]. Meier has served on review panels and advisory boards for the Diet–Heart Study, the University Group Diabetes Program, CASS, and MRFIT, among others. He has drawn on these experiences in writing on problems of safety monitoring and ethics in clinical trials [4,5]. The following discussion took place in New York City on August 31, 2003.

Career beginnings: Princeton, Johns Hopkins, Chicago

Marks: How did you get your start in statistics?

Meier: Well, after graduating from Oberlin in '45, I was accepted at Princeton into their math department, and I decided to study logic. I was talked to by Dr Taylor who was in charge of graduate students. He said "John Tukey has not had any students and

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we're anxious to give him some". Although I was in logic, he said I could study the logic of probability, or something like that. Afterwards, I thought that going in with somebody who had no students before is kind of treacherous – but I didn't think about this at the time. I'm glad I didn't, because John Tukey was the primary genius in my generation. (*Note:* Meier was the fifth student to receive a doctorate under Tukey [6].)

Tukey wanted to get advice from Bill Cochran at Johns Hopkins, who had many students. Cochran proposed an interesting statistical problem about two samples with equal means and unknown, unequal variances which turned into my thesis project.

Marks: How did you get involved with biostatistics? Medicine at the time was an unusual choice for a statistician.

Meier: I had told John how nicely Cochran had written about my work and I thought he was a great guy. John said that I should go with Cochran at Johns Hopkins. I was a little nervous because by and large, biostatistics was not a field with a lot of mathematics in it, and I wished more or less to be a mathematician. Well John insisted, and so I went there.

Marks: What kind of statistical work did you find at Hopkins?

Meier: When I went down there, Cochran said "you'll be okay for six months. Do your work then because after that, people will get to know you and they'll want to consult you all the time". Indeed, that was true. I worked on a very broad range of medical and basic science projects with some very good people.

Marks: You said you had been somewhat uneasy about coming to Hopkins because you wanted to be a mathematician. Is that why you left for the Statistics Department in Chicago?

Meier: I found that what we were doing at Hopkins was teaching graduate students in public health. It seemed to me that they did well after coming to us, and after a while I said "Maybe this is good enough". I probably would have stayed at Johns Hopkins if Cochran had stayed but he decided to go to Harvard. I consulted with a group at the Hopkins main campus and said that eventually I wanted tenure. They said no, and that was the end of that. I went looking and got the job at Chicago and that was the main period of my life.

Marks: I would imagine that was a big jump. In Chicago you had Jimmie Savage working on statistical foundations, and high powered people in sampling theory and doing work with social science – William Kruskal and Leo Goodman.

Meier: You know Harold Dorn, the fellow who invented statistics at NIH (National Institutes of Health)? We wanted to get NIH training grants in statistics at Chicago and Dorn said: "The people I get from Chicago are all good people. People I get from other places are not so good". People there had more grounding in mathematics. You don't want to fear mathematics, you want to study it and make it part of your system. Most places didn't do that.

Marks: Were you the only one at Chicago concerned with medical applications?

Meier: As far as the statistics department was concerned, by and large, yes.

Marks: Were you getting a lot of students?

Meier: I had maybe 12, 14 students. I didn't have 200. The students who came to me were very good. For example, Rick Chappell at Wisconsin has done very well.

The Kaplan–Meier estimator

Marks: You worked on a rather important statistical paper while you were at Hopkins: the paper on what we now call the Kaplan–Meier estimator [7]. It's running more than 30 000 citations, which must make it one of the most cited papers in the biostatistical literature. How did that paper come about?

Meier: Well, the problem of analysing failures which are dispersed in time was an old one. Charlie Winsor was working on it, and came up to Princeton and talked to Tukey about it. [Joseph] Berkson from the Mayo Clinic had written a paper about it, but he hadn't estimated the variance. Somebody asked me how to do it, and I said, "Oh, that's very hard: you have to do this and that and ... ". Then one of my colleagues showed me a Major Greenwood paper on it that opened my eyes quite a bit, and he told me what Winsor had done and that opened my eyes still more. So, I worked on the problem. Jerry Cornfield was working on the problem as well, and he had some different methods from the ones I was developing. Suddenly, Cornfield told me he wasn't working on that problem anymore. That disappointed me, but I think he knew that I had solved it.

Marks: So what was the problem?

Meier: The problem is the one of how you handle censored observations when you are following a cohort of people: early in the study, people die at a certain rate. Some people live a little longer but then die at the same rate. Yet you have only two instead of five years of observation on this second group. What are the effects of these censored observations on your estimates of treatment effects for the group as a whole?

As I was working on it, I wrote to Tukey about the problem, and he told me that Kaplan – another of his students – was doing something kind of similar. I didn't know Kaplan, but I wrote to him about my ideas, including the notion that if you only have two instead of five years observations on some patients, the estimates may be quite biased. Kaplan had thought the estimates were unbiased. He wrote back and said that he had credited the idea of biased estimates to Meier, and sent his paper off to *JASA*.

Well, I got pretty mad and I called John. Ultimately, I wrote to the editor of *JASA* about the situation; by that time, I had estimated the means and stuff like that and not just Kaplan–Meier alone, and I offered *JASA* this as a second paper. The editor wrote back that our readers wouldn't like it if you separate this into two papers. I'd rather you both got together and wrote one paper. I swallowed hard, and I guess Kaplan swallowed hard as well. So, we worked quite hard and at one place he solved a problem that I couldn't solve; other cases I solved problems he couldn't.

Marks: I had not read the original paper until recently. It reminded me of the way RA Fisher's generation introduced new statistical methods. That is, the article is very balanced in describing a variety of approaches to failure–time analysis, and describing the properties of each approach. It's not a paper that aggressively markets Kaplan–Meier as the best way to solve all problems.

Meier: The notion that a research paper ought to say that this is the one thing that you should do didn't occur to us. Both Kaplan and I were students of Tukey, so maybe that spirit comes from Tukey's exploratory philosophy of data and statistical methods.

Clinical trials: Randomization and the polio trials

Marks: Can we talk about clinical trials?

Meier: Well, that's my true love. The notion that randomization could clear away confounders that you did not know about was a great idea. It had been talked about before but not in terms that Fisher had used. Since I was involved with medicine I said, this is great, if you use randomization you could find out stuff you really need to know.

Bradford Hill, who convinced investigators to randomize the UK study of streptomycin for tuberculosis, is very important here [8,9]. He was head of the Department of Biostatistics at the London School of Hygiene and Public Health. Hill was totally involved with medical problems and the people in medicine were attracted by him, saying "Bradford Hill says this." He was a physician and physicians didn't mind him as much as they minded me. Hill's study was randomized, and I thought, "So now we know about streptomycin." I found that extremely attractive and in everything that I did after that, I said "Randomize!"

Marks: What happened when you said that?

Meier: When I said "Randomize" in breast cancer trials, I was looked at with amazement by my medical colleagues. "Randomize? We know that this treatment is better than that one." I said "Not really." Still, people who knew and respected me were astounded that I should want to randomize their patients.

Marks: When did you start doing that?

Meier: I started doing that quite early. And then came the polio field trials . . .

Marks: Let me ask you about the 1954 Salk Polio Vaccine field trials. You've written, very enthusiastically, about this trial. Let me play devil's advocate. Weren't the 1954 field trials very sloppy trials, from the point of view of 'good' experimental design? Half or more of the children were studied with observational controls in states that were unwilling to randomize. Then, you have multiple endpoints: polio deaths, cases reported, paralytic cases, non-paralytic cases, antibody titres . . . . And for some of these endpoints there are issues of ascertainment bias. What would you say?

Meier: Well, first of all, the polio study was the most elaborate trial that was ever done, and you had to do it that way because polio was very scarce. I've not been involved in many trials like that and I've been involved in lots of multicenter studies. Second, the study was randomized in many states. The epidemiologist in New York State decided the study had to be randomized. Well, New York State was a prize; the National Foundation for Infantile Paralysis (NFIP) which ran the study wanted New York. So they said to the other states, you can randomize or you can not randomize; it's up to you. So quite a few states randomized, so nobody knew who was getting vaccine and who placebo. That's great. And then the randomized sites came up with more or less the same results as the places with observed controls. I studied the randomized sites without bothering with the nonrandomized set.

Next, we said, the diagnosis of polio is tricky, but we need to have the entire country's physicians participate, because we can't look over every case where there's some kind of paralysis. So physicians reported the cases they thought were polio according to the protocol, and we accepted those cases. Now, about half those cases were probably not polio at all,

but still, we did have total reported cases, compared with paralytic and nonparalytic cases. And the results were consistent, more total cases and more paralytic cases in the control group.

Marks: So consistency of results mattered?

Meier: No, the measure I rely on is total cases: paralytic cases is good, but not quite the same as total.

Marks: The field trials had an enormous, unprecedented amount of publicity. Did they have any influence on clinical research, that is, did the model of randomization carry over from the field trials to clinical research?

Meier: Well, the epidemiologists unfortunately folded. That is, they wanted to do more clinical trials at this point in time, but then, as clinical trials got popular, epidemiologists saw them as the statistician's job rather than theirs; epidemiologists wanted to do more of the stuff that couldn't be randomized. I wish they had been more alert.

Marks: You wanted to talk about the safety issue with the polio vaccine.

Meier: Yes. I was worried about the safety issue because, before the results were announced, I had a seminar in my department [at Hopkins] with the people involved in polio attending. David Bodian, the Hopkins virologist who worked on poliomyelitis was there and helped us in explaining the safety testing procedures. Jonas Salk had a paper in which he argued that all the virus was inactivated, and that there was no live virus left. Salk had presented data which showed that inactivation behaved in a linear fashion, as if they were following some first-order chemical reaction; he had data on multiple lots of vaccine, 1, 2, 3, 4, 5, ..., 9 which seemed to follow this chemical law. But, the sixth lot was not listed. And so I said that something was wrong. He cut out data in order not to show what happened to some lots. And people read my analysis, and Cochran said something like, "Well, Meier's right, but they have a very good group of people on the NFIP Advisory Committee and I'm sure they wouldn't ignore data, so they obviously had excellent data from the manufacturer."

Well, NFIP did form an advisory committee. And they reformed it five or six times. Each time somebody didn't agree, they dropped them and got somebody who might agree. By the time they were done forming the committee, everybody on it was distinguished, but very agreeable.

Marks: When was this happening?

Meier: This is while the trial is going on. And when Tommy Francis finished the analysis, and said it was ready to report, they had people gather in Michigan, including the Advisory Committee and many others. The results seemed to be excellent, in favour of the vaccine, and the NFIP asked the Advisory Committee to say it approved the vaccine so that vaccination could begin at once.

Albert Sabin MD, who was an NFIP supported researcher, objected. He said that the report itself had not been given to the Advisory Committee in advance. He said that the Committee should at least study the report and then they might vote. "Give us time to read it," he argued. The NFIP gave them two hours. The NFIP was quite powerful. They had anybody engaged in public health, paediatric groups, all supporting the vaccine. Almost everybody said it was an excellent vaccine and it should be immediately released for vaccine injections.

Then, two weeks later, the Cutter incident broke.

Marks: This is after the trial was over, and vaccine was in production, yes? There were a series of polio cases in kids who had received vaccine from lots that were traced back to Cutter Laboratories, one of six manufacturers licensed to produce the vaccine.

Meier: Yes. I looked into this; I got some data from a physician who was working on this, and we found that not only was Cutter wrong, but there were various other companies that had the same polio virus in their samples, although not as much as the samples from Cutter Laboratories.

But because there were so many improperly diagnosed cases out there, and because the other manufacturers went around to various newspapers and threatened to cut their advertising, it was dumped on Cutter. Cutter was responsible because they did things in producing and testing the vaccine they were told not to do. The government also fired Workman, the head of the NIH Bureau of Biologics, and he had nothing to do with it.

So, I wrote this paper about the safety analysis [2]. The NFIP advisory committee then had a meeting to discuss what they should do about Meier's paper. After some discussion, they said "Nothing." I think they were very wise.

Marks: Not a good idea to pick a fight with Meier because that will just call attention to his paper?

Meier: Yes. They were very wise, because while I got congratulations from several polio people very high up, that's all I got.

Marks: How did the *Science* paper get published? Didn't you try to get the analysis published in various medical and public health journals?

Meier: Yes. They said, "You want to go on in biostatistics? You can't do that if you publish this

paper." I said "Really? Look, will you publish it if I submit it?" They said no. But an editor of *Science* – a geneticist named Bentley Glass – was sympathetic. He said, cut out some of the discussion, which doesn't make any difference to the argument, and we'll publish it. So I cut the paper down, and that's how I got it published.

Marks: One of the things about the *Science* paper is that, in addition to analysing the procedures for safety testing, you were very critical of the Foundation and of the Government for not letting people know what the situation is. For 1957, 1958 – the Eisenhower years – this was a very radical position.

Meier: Is it really that radical? People ought to be honest with one another, and the Government hid parts of the story. The White Paper the NIH issued more or less said that but it needed to be said directly [10].

Clinical trials: Ethics and data monitoring

Marks: In 1975, you wrote a paper on ethics and clinical trials [4]. You make an argument there that clinical trials depend not so much on mechanisms of individual informed consent, but on a kind of implicit social contract between Americans, as patrons of research and potential subjects, and the research community.

Meier: This is a paper that I much prize, but I am not sure if it had much of an effect.

Marks: That's a surprise. Why?

Meier: Because of "equipoise." Equipoise is supposed to take care of all the ethical problems. That seems crazy to me, but people are satisfied with it.

Marks: Can you explain why it is that you don't think the notion of "equipoise" works to solve anything?

Meier: Well basically, it says that if anybody sober enough decides that a procedure is questionable, you're able to do a randomized clinical trial. That's crazy. And you have the other situation where almost everybody might agree that this thing is probably going to work; they're not certain, but everybody says it's probably good. There's no equipoise there, but I still think we often must do a randomized controlled trial.

Marks: Because people can be wrong?

Meier: Yes. My notion is that we need to be more proactive – to announce what randomized trials we plan to do, because we have so many things we wish to know. If we did trials, we would save many lives and that would be great. If you decide you're not willing to participate, that's fine, but we should be more proactive.

Marks: How would you go about implementing this? Would you announce the list at the doors of particular institutions? Particular communities?

Meier: Good question. Not everyone should be allowed to do clinical trials. I think we want to be sure they know how to do randomized trials. Say you have a guy who doesn't really know how to do trials, but he wants to do something. I don't think we should permit him to do that. So I guess that means you want to select those places where trials will be done, but a broad selection: every university hospital should be able to do trials. You don't want protection against randomized trials. You want to engage in trials as much as you can.

Marks: So one side of the problem is when you have some data but not enough to be sure, you do a clinical trial. What about when you're doing a trial, and favorable (or unfavorable) data start coming in? How do you handle that?

Meier: Well, first of all, in any clinical trial you might end up with a result where death is increased by 5% or even 10%; unless people are willing to take their life in their hands in that sense, you can't do any clinical trials at all because you would stop too early. So you're interested in this range between least difference and maximal acceptable difference between the treatments. Well, how you handle results in that range depends on what you want to know. Suppose you have enough data to say that it's more than least difference but not enough to say that it's more than maximal difference. Maybe you want to continue the study. Then you reach the maximal difference and then you have to stop. But it's tricky. I've talked about it to various people I respect, and opinions differ on where that stopping point is.

Marks: Where does this decision take place? Does it take place on the monitoring board, or is it part of the rules of the game that you explained to the patient before they come in?

Meier: Absolutely, explain it to the patient, and if the patient trusts you, he will go along into the trial. If he doesn't trust you, he won't, especially if you have death as one of the endpoints. Maybe I want surgery for my breast cancer, but radical surgery is quite a business and I don't think I want that but suppose radical surgery is better. Well, maybe radical surgery is better, I'm not sure, but you may die while in the study. I emphasize *may*. The study will go on until a 5% difference occurs, and as long as you need to prove that radical surgery is better. You – the doctor – explain to the patient exactly what's going to happen. In general, if you're willing to do that, it's better for everyone.

Marks: A whole lot of that argument depends on trust of the physician. I can imagine two problems with your position. First, ours is a society which has become permeated with mistrust of medical researchers, at least in many communities, and two, some of that mistrust comes out of a history of researchers abusing trust.

Meier: Well, basically, that's because researchers don't tell them everything. That's my notion: total disclosure.

Marks: Does informed consent cover "total disclosure?"

Meier: Not really. The idea that IRBs pass on what we do is good. But the way we handle informed consent is to say, this explanation is too difficult, too much for a patient to absorb: tone it down, change the language, etc. What you want to do is to explain things to the patient and then have him take it home. Not accept it [consent] if he doesn't take it home so he can read it at leisure.

Marks: Have you been on steering committees or data monitoring committees where you've insisted on that pause between presentation and consent?

Meier: I have been on the IRB and insisted that they do that.

Marks: And your colleagues on the IRB went along? I'm thinking that there seems to be a tremendous anxiety about enrolments, and getting on with the job.

Meier: Well, IRBs do think that if you want the patient to read it while you are standing there, it's alright. My notion is that it's not alright.

Marks: Data monitoring committees were a big innovation in the way clinical trials are conducted. How have they affected the way researchers think about the conflict between patients enrolled in a trial and the community of future patients who might be affected by what the trial says about treatment for their disease?

Meier: Well, data monitoring committees, for example, have said, we're finding no profit in this treatment, so it should be ended. I think data monitoring committees have sometimes been wrong in terminating. But by and large, people settle down with the Lan–DeMets criteria and that's OK.

Clinical trials: The UGDP

Marks: The University Group Diabetes Program was one of the first large trials to encounter this problem of early termination, way before data monitoring committees came into existence. [NB: The UGDP tested the efficacy of several oral hypoglycemic agents versus placebo in adult-onset diabetes.]

Meier: Well, the UGDP was initiated by Chris Klimt; what the UGDP said was that the difference between treatments in total deaths was not significant but the difference in coronary deaths was significant for tolbutamide. Chris had Jerry Cornfield with him, who said they should stop using the drug. As I looked at it, it seemed "not quite." That is, total deaths are fairly well measured, but coronary deaths, especially if you already know the assigned treatment, may not be well measured. I don't really trust coronary deaths.

Marks: You were on the Biometrics Society committee which reviewed the UGDP [10]. That committee ultimately supported the UGDP's decision to stop the trial, saying that the study "raises suspicions [about tolbutamide] which cannot be dismissed." The Biometric Society committee was convened because the study's findings were under heavy attack.

Meier: Yes, the study was attacked by Lou Lasagna, Alvan Feinstein, the Joslin Clinic.

Marks: Did your report convince anyone?

Meier: Well, we persuaded the NIH that this was a good study, and they supported more work by Klimt, which was good. But patients and doctors? Well, my father had heart disease and diabetes and I told him the drug may increase heart disease – why don't you switch from tolbutamide to another drug? His doctor said well, maybe. But when we published the UGDP, my father said he was going to switch medications. I think the doctor was upset that my father wanted to switch drugs. He said, well, you can do what you want. My father died of his heart disease but I think switching drugs made him last a few more years . . . who knows?

Marks: You're a big fan of access to data. You want people to have access to as much data as possible. But in the UGDP case, they published so much data that the critics began taking advantage of this. They found that this table didn't agree with that table, or that MY clinic didn't have a problem with tolbutamide. Is there such a thing as too much access to data?

Meier: I don't want release of the data until a study is done. But after that, I'm in favor of releasing everything and telling people you can look at everything. You have to expect that if a study says a drug house's drug is no good, people will criticize that study, with the drug house's support. But I think we have to publish our data. Otherwise, you'd just publish one thing – it's significant. We once had a notion that you wanted to publish everything in a clinical trial two years after it was over.

Bridging disciplines: SCT, teaching and foundations

Marks: Were you involved in the founding of the Society for Clinical Trials?

Meier: Yes, Chris Klimt decided that we should found it. That is, we had a meeting every year of the people involved in clinical trials and after the third year he said why don't we form a society?

Marks: What was the society supposed to do that couldn't be done at ENAR or the Biometrics Society?

Meier: Well, they had too many things to do, for example, notes on clinical trial design would not be of interest to these other people. We were in favor of ENAR and other groups but we needed our own society. I think it has been quite successful.

Marks: Could we talk about physicians and statistics? Did you teach medical students at Hopkins?

Meier: At Hopkins, we had a marvelous Biostatistics Department, but one thing they would not do is teach medical students.

Marks: Was that the department's choice?

Meier: It was the department's choice because the arrogance of medical students was too much for them. The students didn't believe statistics and they told the school that they didn't believe them and so on. Maggie Merrell was a marvelous teacher; absolutely wouldn't teach medical students at all.

Marks: And at Chicago?

Meier: At Chicago, the students all around the university learned a little about statistics, and I taught a half credit course, ultimately within the Department of Physiology and Pharmacology. And that worked okay for a while. It's interesting – I worked like crazy in order to make this possible. But freshmen, sophomore medical students, they had no interest in statistics. When they get where they really wanted to use statistics, in their fellowships, they have to do it and so I taught the fellows. They were very good.

Marks: Is there any place that you can think of that's had success in integrating statistics into the training of medical students? How can you do anything without looking at the data, and how can you look at data without understanding some things about statistics?

Meier: We had a seminar at the joint statistical meetings two years ago, with a group of talks on teaching medical students. Ted Colton, Boston University, was there. He said that he had been quite successful teaching everyone except for medical students. And other people repeated that. If Ted Colton can't succeed, who can? It's odd we have not been successful with medical students at all.

Marks: When you were growing up as it were, there were a lot of people who were very big figures in statistics who are spending their time arguing about the foundations of statistical theory: Neyman and Pearson, Fisher, Savage. You stayed out of this. Why?

Meier: It's interesting. The idea that one invents a prior repels me. Invent a prior? Why should anybody believe me? However, I find that if people have a Bayesian method for doing something, it may have a non-Bayesian interpretation. That's pretty good. Wald found that any study that you want to have follows Bayesian rules. And also the physicist in England [Harold Jeffreys] who wrote on Bayesian methods. He said you want flat priors for the main effect and logarithmic priors for the variance. I might have adopted his method if I had learned about it earlier. But John [Tukey] taught me statistics; he didn't teach anything about Bayesian analysis. John simply didn't talk foundations at all.

Marks: Looking back over your career, what are the important methodological advances in design or analysis that you would say makes some difference from the way you were taught in graduate school?

Meier: Well, I've talked about Tukey of course. By and large I don't think anything really has changed except the computer. The computer expands our range tremendously, but I think we're doing the same thing.

Marks: And what are you most proud of in terms of your own work or legacy so far?

Meier: Well, it would have to be my promoting of randomization. For a fairly long time randomization was not thought of so highly. I defended randomization every chance I got, and I had a fair number of chances. Two years ago a very distinguished statistician told me that I had a major influence on the Food and Drug Administration's policies on RCTs. I don't know how true that was, but if so, it would be something of which I am very proud.

Marks: Thanks so much for spending all this time.

Meier: I very much want to thank you for visiting me, and I'm honored to be the first interviewee for the Society for Clinical Trials' new journal.

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