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A Conversation with Allen J. Wilcox

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Abstract

Allen James Wilcox was born on 30 September 1946 in Columbus, Ohio. He studied medicine at the University of Michigan, graduating in 1973, and after a rotating internship completed a master's degree in maternal and child health (1976) and a PhD in epidemiology (1979) at the University of North Carolina in Chapel Hill. After graduation, he went to work at the National Institute of Environmental Health Sciences (NIEHS, one of the US National Institutes of Health) in Durham, North Carolina, where he has spent his career. He developed a research program in reproductive and perinatal epidemiology, a relatively unexplored area at the time. His studies include the Early Pregnancy Study, which documented the extent of subclinical pregnancy loss in humans and established the fertile days of a woman's menstrual cycle. He served as Chief of the Epidemiology Branch from 1991 to 2001, and as Editor-in-Chief of the journal *EPIDEMIOLOGY* from 2001 to 2014. His textbook, *Fertility and Pregnancy – An Epidemiologic Perspective*, was published by Oxford University Press in 2010. He was elected to the American Epidemiological Society in 1989, and served as its president in 2003. He also served as president of the Society of Pediatric and Perinatal Epidemiological Research (1996) and the president of the Society of Epidemiological Research (1998). He holds adjunct teaching appointments at the University of North Carolina, Harvard University, and the University of Bergen (Norway), which awarded him an honorary doctoral degree in 2008.

INTERVIEW

AMJ: How did you find your way to epidemiology?

AJW: My path was pretty crooked. I went to medical school at the University of Michigan. Memorization is not my thing, and I was a mediocre student. I took some courses in the public health school, and one that grabbed me was a demography course. I liked the way that data on just births and deaths were enough to construct complicated pictures about the health of a population.

After my internship, I did a master's degree in maternal and child health at the University of North Carolina in Chapel Hill. At the end of that year, I was still thrashing around wondering what to do next. One of my faculty advisors said, "I think what you want to be is an epidemiologist." That was a surprise to me. John Cassell was the chair of the

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Epidemiology Department, so I went to see him and asked “Is there a place for me here?” He said, “Sure. Take some courses, go to seminars, see what you think.” Within a month I realized I had found my calling.

AMJ: Your first (and only) job has been at NIEHS. What was it like when you first arrived?

AJW: In 1979 the entire epidemiology branch fit around a small picnic table. Walter Rogan was there, and Richard Everson, and Dale Sandler. They’re all smart people, and I learned a lot from them. In a way, my education as an epidemiologist was only just beginning when I started work.

AMJ: How did the Early Pregnancy Study¹ come about?

AJW: It was a combination of serendipity and golden opportunity. I arrived at NIEHS shortly after the toxic-waste disaster was discovered at Love Canal. One of the health problems at Love Canal was an apparent increase in miscarriages. Miscarriage risk had not been much studied by epidemiologists, and it seemed like a good outcome to explore.

Around that time I met Alan Treloar, who had retired to Chapel Hill. Alan had done a prospective study of menstrual cycles in college women – I believe it’s the longest-running cohort study ever done.² He enrolled female college students in the 1930s, many of whom kept menstrual diaries until menopause. Most important for my interests, the women recorded events that interrupted their periods – including miscarriages. I proposed to Alan that we re-contact these women to see how well they remembered their prospectively recorded miscarriages. This seemed useful since most epidemiologic studies ascertained miscarriage through women’s recall.

Alan Treloar had good intuition about field studies. One of his innovations was to collect a whole year’s worth of menstrual diary information on a single card that fit in a woman’s purse. He was a great advocate of simplicity.

AMJ: How has that influenced you?

AJW: Treloar’s approach clearly influenced my own approach – prospective pregnancy data collected daily. My question was a bit different, however. I became interested in measuring how much pregnancy loss might occur before women even know they are pregnant. The time was ripe to address this question because excellent pregnancy tests for the pregnancy hormone hCG were being developed. Through NIH contacts, I met Bob Canfield at Columbia University, who had the most sensitive and specific hCG test available anywhere. By a stroke of luck, Bob was a laboratory expert who also understood epidemiology, and he was very supportive of my proposed project. He argued for the collection and analysis of daily urines from women who were trying to become pregnant. Earlier studies had tried to be more efficient by collecting samples on a limited basis -- but those studies ran the risk of missing transient pregnancies. Bob knew that assaying daily samples would be a huge burden on his lab, but his willingness to take this on was an incredible asset for our study.

We also had a fantastic study manager, Joy Pierce, who fully understood the importance of what we were trying to do. And then there were the participants themselves: women trying

to get pregnant are especially motivated to pay attention to what's going on with their bodies. We had incredible cooperation from the participants.

By another stroke of luck, two of my colleagues at NIEHS – Donna Baird and Clare Weinberg – became invaluable collaborators. Donna has a deep understanding of reproductive biology, and Clare of course is a gifted statistician. Both brought essential insights about biological mechanisms and testable hypotheses. Over the years, we've been able to add layer after layer of laboratory data and construct new variables that allow further analyses. It's been an adventure.

AMJ: You've worked with your collaborators for a long time. What's the key to that success?

AJW: We so much need colleagues we trust, who can tell us when we're wrong or off on a tangent. I've benefitted from excellent colleagues over and over again – not only Clare and Donna, but Rolv Skjaerven and Rolv Terje Lie and many others.

In my experience, an important part of working with collaborators is to be as generous with them as possible. By that, I mean giving them full credit and more for their contributions. (Even then, I probably haven't given them all the credit they deserve.) Collaborators appreciate this, and will return the favor. The ideal situation is for everyone to be looking after each other's interests, and then no one has to guard their own.

AMJ: How have you balanced work life and outside life, family life?

AJW: My wife and I were medical students together and had surgery rotations at the same time. It was a disaster – nobody to cook dinner or do the laundry. We realized that if we wanted to have any kind of home life, we had to have jobs that didn't require eighty hours a week. I've always appreciated working at NIH, where I could set my own boundaries. I love my work, but there are a lot of other great things in life too.

AMJ: What are some of your other interests besides epidemiology?

AJW: I've lived in Durham for forty years. It's a medium-sized city with a lot of opportunities for citizen involvement. About fifteen years ago, I helped start a nonprofit to develop a park in downtown Durham, and due to the work of a lot of terrific people it's flourished.

AMJ: How did you get to be the editor of EPIDEMIOLOGY?

AJW: Not by planning. I always liked the process of reviewing papers -- trying to judge a paper's contributions, and helping authors get their message across. But there didn't seem to be any prospects of me actually becoming an editor-in-chief – of being able to shape a major journal. I resigned myself to that.

Then in 2000, my phone rang and it was Ken Rothman. Out of the blue, he asked "How would you like to be the editor of EPIDEMIOLOGY?" I said, "Absolutely. No, wait. Give me twenty-four hours to think about it. But yes, I'm going to say yes." And I did.

AMJ: How has the field changed during your tenure as editor?

AJW: Lots of ways. Topics come and go. When I first started, the effect of air pollution on heart disease was just a hint, and then data came in a flood. There's a lot more epidemiology coming out of developing countries now— particularly China. I think epidemiology in general is more diverse, which is a good thing.

AMJ: What's your most underappreciated paper?

AJW: I suppose every researcher thinks some of their work is under-appreciated. In one of my favorite papers that hasn't gotten much attention, we looked at the relationship between timing of intercourse and ovulation.³ We found that women were increasingly likely to have intercourse on their fertile days, just before ovulation. Reasonable critics said "Of course these women had more intercourse around ovulation – they were trying to get pregnant." So we tested the hypothesis with data from women who were not trying to get pregnant, and the pattern of intercourse around ovulation was exactly the same. Then the question arises: what is affecting the timing of intercourse?

In some ways, a rich dataset is like a laboratory for epidemiologists. It's a place where we can do internal "experiments" to test our hypotheses. The richer the dataset, the more experiments we can do. In this case, we wanted to distinguish between two hypotheses: Is there more intercourse around ovulation because of effects on libido? Or might intercourse actually help trigger ovulation?

After a lot of futile struggles to get at this question, I realized we had an instrumental variable to work with: day of the week. Couples have more intercourse on Saturday and Sunday than during the rest of the week. If intercourse were in any way stimulating ovulation, then we should see a blip in ovulation after the weekend. Sure enough, there was a blip – although not strong enough to be entirely persuasive. Then Clare suggested that we stratify couples by the strength of their weekend preference. The couples who had intercourse primarily on weekends were in fact the ones who had ovulation primarily on Monday or Tuesday. So much fun. We can't do experiments in observational data, but sometimes we can come close. We've been hoping that someone would test this in a clinical trial, but I don't know that anyone has ever tried.

AMJ: How have you chosen the research questions that you've addressed?

AJW: For me, it has to be a question I care about. There are so many boring parts about doing a study. If you're doing it only because somebody wants you to, or because you feel some obligation to do it, it's hard to give the day-to-day tasks the commitment they need.

AMJ: What was it like to write your textbook?⁴

AJW: I was lucky to study perinatal epidemiology when there wasn't much work being done in the area. It gave me the chance to formulate a general approach that made sense to me. But individual papers can do only so much to convey a general approach. I wanted to give people a broader picture, to let them see how the various stages of reproduction fit together. Reproduction is a whole package that's really fascinating, and a researcher needs to

understand that package even if tackling only one small part of the continuum of reproduction. That led me to the idea of a textbook. I started by teaching short courses in the summer epidemiology programs, and after a few years, I got to a point where I felt like okay, I'm ready to write a book.

I took a year off work to write, and it was pure pleasure. I would sit down at the computer after breakfast and I'd forget to have lunch. At the end of the day, I'd pack it all up reluctantly and go back to it the next morning. I loved tracking down primary sources, seeing if what I had been saying all these years was really true, contacting people to confirm anecdotes. I didn't want the book to be a series of facts. As I said, I am terrible at memorizing. Facts aren't as important to me as the process of how we get to them. I wanted the book to be something that would engage people in the excitement of how research is done.

AMJ: What's the biggest risk you ever took in your career?

AJW: Probably it was trusting that there was something out there I wanted to do when I had no idea what it might be. After med school, I stayed home for a year to take care of our newborn while my wife did her internship. One of my med school professors told me I was getting off the train and I wouldn't be able to get back on. But it didn't make sense to me to stay on a train just because it was moving. When I finally stumbled on epidemiology, I realized how lucky I was to have had the opportunity to wander as I had.

AMJ: What do you want to be remembered for?

AJW: A presumptuous question! If there's anything, it would probably be for trying to bring epidemiologic tools to perinatal epidemiology and, conversely, to bring the insights of perinatal epidemiology to the wider field of epidemiology. Perinatal epidemiology required new methods and new approaches. Those methods in turn could help shed light on broader epidemiologic concepts.

One good example is birth weight. Low-birth-weight babies have high mortality, and low birth weight was regarded for many years as a cause of perinatal mortality. However, there is a paradox -- small babies from women in high-risk groups, such as smokers, actually have *lower* perinatal mortality than small babies of non-smoking mothers. I realized early on that this paradox undermined a causal role of birth weight in neonatal mortality.

With a series of collaborators over the following years, I wrote papers that increasingly honed in on the problem, but without really solving it. Then a seminal paper by Greenland, Pearl and Robins in 1999⁵ introduced collider bias as a problem not widely recognized in epidemiology. I came to understand that collider bias was at the root of the birth weight paradox. In 2006 I wrote a paper with Olga Basso and Clare Weinberg in which we showed that collider bias could explain this paradox.⁶ In the same year, Sonia Hernandez-Diaz and her colleagues wrote a paper basically pointing out the same.⁷ Olga then suggested that if collider bias were messing with birth weight, it's probably happening with gestational age as well.⁸ We're working on another paper right now on this topic -- it's a surprisingly rich area.

Not long ago, I got an email from Judea Pearl saying, “I’m writing a book on causal inference and I think birth weight is a good illustration of collider bias. Would you talk to me about how you came to this?” So much fun, that perinatal epidemiology can help inform epidemiology as a whole.

AMJ: What advice do you have for students or junior colleagues?

AJW: I’m concerned about bad behavior in science. People falsify their data, papers are retracted – it’s deeply disturbing. Honesty is the absolute bedrock on which we stand. How is it that some researchers go so far wrong?

Admittedly, we all have complicated motives for what we do. We want to impress our colleagues, get funding, be famous. But still, practically every researcher brings some idealism to their task. That idealism needs to be protected, and cultivated. Idealism can so easily get crowded out by the day-to-day problems we have to deal with.

There are at least a couple of things we can do to protect our idealism. One is to choose research questions we really care about. This echoes something I mentioned before. If we genuinely want to know the answer to a question, then we are more motivated to do what’s necessary to get to that answer. Also, once we see our results, we need to resist judging the results by what we think might be the public health implications. It shouldn’t matter. What matters is that we express our results as faithfully as we can from our imperfect data. The truth is what will lead to better public health – not what we think the truth ought to be.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SDC Allen Wilcox’s curriculum vitae is available with the online version of the article at [insert link].

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Biography

Dr. Anne Marie Jukic is an Assistant Professor at the Yale School of Public Health with a broad interest in perinatal epidemiology. Her current research focuses on fertility and early pregnancy – a trajectory firmly established by her 10-year collaboration with Dr. Wilcox. Working with Dr. Wilcox has been an immeasurable honor, and she cannot imagine where she would be without the influence of his wise, generous, and insightful mentoring.