Promoting Innovation in Pediatric Nutrition

Dennis M. Bier

USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX, USA

Abstract

Truly impactful innovation can only be recognized in retrospect. Moreover, almost by definition, developing algorithmic paths on roadmaps for innovation are likely to be unsuccessful because innovators do not generally follow established routes. Nonetheless, environments can be established within Departments of Pediatrics that promote innovating thinking. The environmental factors necessary to do so include: (1) demand that academic Pediatrics Departments function in an aggressively scholarly mode; (2) capture the most fundamental science in postnatal developmental biology; (3) focus education and training on the boundaries of our knowledge, rather than the almost exclusive attention to what we think we already know; (4) devote mentoring, time and resources to only the most compelling unanswered questions in the pediatric sciences, including nutrition; (5) accept only systematic, evidence-based answers to clinical questions; (6) if systematic, evidence-based data are not available, design the proper studies to get them; (7) prize questioning the answers to further move beyond the knowledge limit; (8) support the principle that experiments in children will be required to convincingly answer clinical questions important to children, and (9) establish the multicenter resources in pediatric scientist training, clinical study design and implementation, and laboratory and instrument technologies required to answer today's questions with tomorrow's methods.

Arguably, truly impactful innovation can only be recognized in retrospect. Further, allowing for the most expansive meaning of innovation, developing algorithmic paths on roadmaps meant to lead to innovation are unlikely to be successful because true innovators do not generally follow established routes. Nonetheless, I will take the position that academic Pediatric Departments can provide the conditions necessary to foster environments where innovation will flourish. Possible options include the following.
Correct Common Misperceptions about Pediatrics. In many areas of medical science, pediatrics is viewed as an inadequately compensated subspecialty that feeds babies, promoting breastfeeding practices and magical unproven rituals for the introduction of complimentary postweaning foods. Pediatricians are also seen as spending their time giving infants immunizations against classical childhood illnesses and providing antibiotics for largely self-limiting viral infections. Later in childhood and adolescence, they are perceived as the mediators (and medicators) of learning problems among mother, child and teacher and as the medical professional providing some psychosocial counseling to teens. These are critically necessary and highly commendable functions, and training programs would be remiss if they did not adequately prepare pediatricians for delivering these essential services. Nonetheless, I might argue that these perceptions diminish the choice of pediatrics as a career by many medical students who want to be at the aggressive, leading-edge 21st Century science. To be sure, the perception is not the reality, but we pediatricians have, apparently, not adequately communicated the opportunities of pediatric sciences to medical students. Moreover, the constraints placed on the structure of pediatric training programs by credentialing and licensing requirements (at least in the United States) are now such that the vast bulk of residency training is devoted to the practical aspects of what we ‘know’ (or think we know). Little time is left for development of investigative minds. Arthur C. Clarke’s Second Law reads ‘The only way of discovering the limits of the possible is to venture a little way past them into the impossible’ [1]. To encourage the thinking that will promote young scientists’ discovering innovative ways beyond the boundaries, we need to spend more time teaching the limits of our knowledge, focusing on what we do not know rather than on what we ‘know’.

Pediatrics Needs to Be the Dominant Force in Human Developmental Biology. For a significant part of the 20th Century, pediatrics was the focal point for research in human developmental biology. Further, pediatricians have long appreciated that development does not end at birth, but continues throughout childhood both at the organ and system levels and in the realms of neurodevelopment and psychosocial maturation. More recently, however, the field of developmental biology has largely focused on embryonic and fetal development following dramatic advances in the fundamental molecular regulation of the developmental processes in these areas. Most of the work takes place outside of pediatrics. Further, Departments of Pediatrics have been slow in capturing a dominant position in uncovering the basic processes of postnatal development and investigating the direct consequences of aberrant developmental regulation on the pathobiology of adult diseases, a now well-recognized phenomenon [2–7]. Thus, pediatric scientists need to take the lead in promoting recognition of the fact that development does not end at birth and in developing the investigative tools that will allow us to discriminate real developmental programming effects from the pari passu changes in
age and size, etc. Furthermore, since the development of behaviors in childhood has profound consequences on attempts to modify behaviors both during childhood and later in adult life, pediatric scientists must (a) promote the growth of the developmental behavioral field in pediatrics and (b) apply the same level of fundamental science and scientific methods within the field of childhood behavioral development. From the perspective of pediatric nutrition and in the context of the Worldwide prevalence of obesity, basic scientific data on how appetite, satiety and food preferences develop in childhood and are modified (or not) as the child progresses into adulthood are woefully limited.

Ask Compelling Questions. Jacob Bronowski said ‘that is the essence of science: ask an impertinent question, and you are on the way to a pertinent answer’ [8]. Steve Butler likewise said that ‘behind every great answer is a greater question’ [9], a proposition that I firmly believe. As a complement, I also argue that mediocre questions attract mediocre scientists. The quality of the question drives both the quality of the scientist as well as the quality of the innovation. Furthermore, it is likewise the obligation of senior mentors to foster the development of great questions by trainees. In an New York Times interview [10], Tim Brown, Chief Executive Officer of IDEO is quoted as saying ‘... you don't know where the best ideas are going to come from... so you’d better do a good job of promoting them when they come and spotting them when they emerge... I’ve gone to great lengths to encourage what I call an emergent culture... where people understand that it’s essentially their responsibility to have good ideas... If you’re focusing on the wrong questions, you’re not really providing the leadership you should... the great leaders... somehow had the ability to frame the question in a way nobody else would have thought about’ [10].

Question the Answers. Limit complacency with one’s findings, especially if they agree with one’s preconceived notions. Philip K. Dick addressed this issue when he wrote ‘Reality is that which, when you stop believing in it, does not go away’ [11].

Incisive answers always lead to new compelling questions. Bernard Haisch said ‘Advances are made by answering questions. Discoveries are made by questioning answers’ [12].

Question the Experts. Expert opinion is at the lowest level of an evidence-based hierarchy. Almost all expert committee reports and narrative reviews currently fall into this category. In 1931, during the rise of Nazi Germany, Albert Einstein was criticized in a tract entitled ‘One hundred authors against Einstein’ [13]. In his now classical response, Einstein replied ‘If I had been wrong, one author would have been enough’ [13].

Provide an Environment That Allows for Mistakes at the Cutting Edge. One cannot expect to extend the limits of current knowledge without making mistakes while trying to push through the boundaries. Innovation requires risky hypotheses. In turn, taking risks will surely lead to some mistakes.
These should be viewed as learning opportunities rather than failures. Niels Bohr said that ‘An expert is a man who has made all the mistakes that can be made, in a very narrow field’ [14].

*Don’t Settle for Maybe.* Follow Mark Twain’s dictum ‘Supposing is good. Finding out is better’ [15]. It is difficult to do research in children for both ethical and practical reasons. For those reasons, one should be committed to convincingly answering the questions asked in any pediatric clinical research study. In the era of evidence-based medicine, it is neither adequate nor ethical to conduct underpowered studies with inadequate primary end point variables. Similarly, one should exercise caution about underpinning theory or driving practice with observational data. Associations uncovered in such studies cannot prove cause and effect, but only suggest ‘maybe’. As Werner Heisenberg stated ‘...since the measuring device has been constructed by the observer... we have to remember that what we observe is not nature in itself but nature exposed to our method of questioning’ [16]. C-reactive protein (CRP) provides an example of how the method of questioning exposes different views of Nature. The literature is filled with observational studies showing the association of elevated CRP, a marker of inflammation, with an increased risk of heart disease, cancer and other pathological end points. Causation is often implied. When, following Mendelian randomization that takes advantage of common single-nucleotide polymorphisms that result in elevated CRP levels, cardiovascular and cancer risk data are observed from the different perspective, it becomes clear that elevation of CRP per se is not associated with ischemic heart disease or cancer [17, 18]. Thus, it is highly unlikely that elevated CRP levels themselves are causal agents in the increased risk observed in traditional observational studies. The fundamental principles of scientific evidence are the same in all the sciences. Among these are an explicit question, an explicit end point variable, isolation from confounding variables, randomization, intervention, replication and prediction. Pediatric clinical studies should be devoted to providing the highest grade evidence possible from every experiment conducted in children. Often, randomized controlled trials or meta-analyses unmask results that are contrary to conventional ‘wisdom’ and are heavily critiqued as not being too narrowly defined for decisions in related clinical circumstances. However, if a randomized controlled trial or meta-analysis is properly designed and conducted, the answer is correct for the specific question asked. If clinicians want the answer to a different question, they should design a similar study that is specifically directed at the question they want answered, providing new data for integration rather than merely critique of properly collected data that does not address their question.

*Provide an Environment That Supports Research in Children.* Based on the scientific hierarchy of evidence, it should be obvious that one can not be convincingly sure of answers to clinical questions in children without doing experiments on children. Why should our standard for evidence in children
be less than that in adults? I am not suggesting that children be subject to unnecessary risk, but, in my opinion, there is a current prevailing atmosphere that has set the bar of ‘minimal risk’ so low that it is almost impossible to conduct many safe experiments, or obtain the minimally invasive samples, necessary to convincingly answer important questions.

*Improve the Quality of the Methods Used in Nutrition Research.* Arthur C. Clarke’s Third Law states that ‘any sufficiently advanced technology is indistinguishable from magic’ [1]. Few nutrition methods are magical and few fields of fundamental biology today use methods as old as many that are routinely used in nutrition research. 20th Century methods lead to 20th Century answers. While many tried and true methods remain appropriate for certain questions, old methods often address a level of what was once mechanism but is now only upgraded phenomenology, providing now new insight at the current level of mechanism. Furthermore, few, if any, cutting edge fields in biology propose ‘validating’ demonstrably inaccurate and imprecise methods against other demonstrably inaccurate and imprecise methods, a practice common with, for instance, various dietary intake instruments used in nutrition research.

Since most of the ‘action’ in biology occurs within cells rather than in readily accessible compartments like the vascular system, focus should be on methods that interrogate inaccessible compartments noninvasively. These include magnetic resonance spectroscopy and functional imaging methods such fMRI, along with corresponding stable isotope tracer approaches that employ compartmental modeling [19]. Additional investment should be made in nutrigenetics, nutrigenomics, metabolomics and epigenomics [20], all new approaches that will help clarify the basic systems biology of nutritional regulation of metabolism and function. One goal of nutrigenetics is to use information on DNA sequence variation to elucidate nutrient gene interactions and permit better identification of variable individual responses to diets. Nutrigenomics and epigenomics will allow dissection of how environmental signals (i.e. food, in the case of nutrition) are transduced to alter gene expression [20]. One ultimate goal is individualized nutrition, although one must be only cautiously optimistic. For example, the promoter region of a single gene, the phosphoenolpyruvate carboxykinase gene, contains an exceedingly complex number of regulatory elements [21, 22]. It is difficult to fathom, then, how one might untangle the unimaginably immense complexity of regulatory interactions that might occur among all nutrients and all genes of the human body to arrive at individualized solutions.

Unfortunately, many Departments of Pediatrics and Departments of Nutrition do not have the financial resources necessary to upgrade the technologies available within the Departments. In 2008, only 23 Departments of Pediatrics in the US received more than USD 10 millions in research grants from the NIH, and 20 received less than USD 1 million. [23] Similarly, only two university Departments of Nutrition received more than USD 10 millions
in research funding from the NIH in 2008, and most were awarded less than USD 5 millions [23].

**Invest in Multicenter Resources.** Given the tools necessary to answer 21st Century questions with 21st Century methods and the limited instrumentation, intellectual capital, and subjects available within most individual Nutrition or Pediatrics Departments, it is imperative that such departments invest in the development of multicenter resources that complete and complement the resources available within a department. First, these investments should be directed at developing resources to train pediatric nutrition scientists, since very few individual Departments of Pediatrics have the basic science intellectual capital resources necessary to train such scientists at state-of-the-art levels. Secondly, shared investments should be made to develop or support technology resources that include the instrumentation for the technologies mentioned above, as well as high throughput sequencing, bioinformatics, nutrient biomarkers, and related new methods for answering fundamental questions in nutrition. Third, since few individual Departments of Pediatrics have access to the number of subjects/patients necessary to convincingly answer most outstanding clinical nutrition questions, it is also imperative that multicenter clinical subject resources be promoted, along with the necessary statistical, bioinformatics, core laboratory, safety monitoring and compliance resources required to conduct the large-scale clinical studies that must be done to confidently settle nutritional questions important to the healthy growth and development of children.

**References**

Discussion

Dr. Ivarsson: I want to come back to the question you raised about different study designs. I agree that experimental studies as randomized control trials are terribly important. However, it is required that all studies, regardless of design type, are carried out with a high quality in every step, which is not always the case. In the field of pediatric nutrition, a lot of knowledge could still be gained by using an observational study design. I am thinking of both observational analytical studies as the case-referent and cohort designs, as well as the ecological design with aggregated data. I agree that the ecological design can never prove causality, but it can be used to generate hypotheses and thereby push research areas forward. In my opinion, observational studies in general are underutilized, and that is especially true for the case-referent and cohort designs. Observational study designs take advantage of the heterogeneity within and between populations both with respect to exposures and outcomes, and through collaborative studies across several countries, and even continents, we could increase knowledge in several different research fields, and also within pediatric nutrition.

Dr. Bier: I don’t disagree with that, but at the end of all of those kinds of studies what you have is a hypothesis, and that’s great. So you don’t get causality, and if you sell it as associations and a reasonable and highly plausible hypothesis, that’s fine; but what is done pretty much by the press to a great extent but also among a very large number of serious epidemiology departments, for example, is to say ‘it’s only an association, of course it’s not causal’, but you wouldn’t be interested in associations unless you thought it was causal, otherwise who would care? So it’s sold frequently as causal.
Dr. Ivarsson: I don’t completely agree. Epidemiological observational studies, especially with the cohort design, can also allow for causal inferences provided they are analyzed with advanced biostatistics and taking knowledge about biology into account. Then, it is possible to draw causal inferences. I would argue strongly for that.

Dr. Bier: Causal inferences, yes, the key word there is inferences, I agree with that. And, by the way, advanced statistics to me may have a different meaning than to you. It means I need complicated mathematics to make a more complicated model to fit what I found the associations to be.

Dr. Singhi: I think you raised the very important issue of how to get young pediatricians into the research. I fully agree with you that we should let them ask questions, and even if they are absurd sometimes they would raise some very pertinent researchable issues. The question that I have is how in a particular department of pediatrics you would involve young pediatricians to get into the research in a concrete way. Would you give them a direction in a particular field of research or you would let them develop their ideas, because first you have to start with one department and then probably move on to network training, you have to have this trend to have that network absorbed into that research.

Dr. Bier: Thirty years ago, in American departments of pediatrics the house staff trainees had time to connect with a particular specialty mentor to undertake small research projects, and it was very common to have residents leave their residency with a publication or things of this sort. The way the boards have been restructured now, they require almost every minute of the resident’s time to be taken up by the necessary clinical care activities, so there is no time anymore for that. The residents who do it, and there are some, do it on their own time. But that’s what has been missing, we have lost this, so it’s very hard now to get fellows who have had some exposure. It seems to me that the main job of the pediatric faculty member is to identify the resident who seems to be interested in his/her specialty, who is interested in how he/she works and then start discussing together what some of the really compelling questions are and the possibility to design a fellowship for that purpose. You have to get them interested.

Dr. Singhi: Would you say that there are grants given for doing research?

Dr. Bier: Again, I can only speak for the US. I haven’t been on the subspecialty board, but my former department chairman who is one of the most aggressive research chairmen in the country, told me repeatedly that he could not get a change in this when we needed some residents to be more engaged in doing research. Now if he was unable to do that, it has to be very hard now to get fellows who have had some exposure. It has to be very hard to do, Dr. Greer do you want to comment on that?

Dr. Greer: The fellowship training programs in the US are a miserable failure right now in getting young investigators into research. We stress during their training that they have to produce a significant publication, which almost never happens even though it is a requirement. It’s similar with residency training programs; the residents have little to no time to participate in a significant research experience given the limitations in the time they can actually work. Their clinical training consumes all of their time. It’s pathetic, and yet the regulations and requirements for training keep increasing; at the same time the total number of work hours continues to decrease.

Dr. Bier: The way this has been happening over the last two decades or so has created a level of junior faculty in many departments who have no research funding because they went through the system so they can no longer support the fellows who are coming to do the new research. We have already a serious research gap in pediatrics, and unless it’s changed we are going to be in big trouble, and if we are already in trouble we are going to be in real trouble in a little while. I don’t know if other people in other parts of the world would speak on this because my experience is only limited to the US.
Dr. Gibson: The NIH grants in the US are way smaller than I thought they were, and if you did a quick calculation you could see that each project was probably in the order of USD 200,000 or 300,000 which you can do very little with, we have had experience with that. The other thing you have highlighted that I was really impressed with is the sort of the mythology about nutritional research. You can’t randomize breastfed babies for example; you can within breastfeeding of course, and you can do things to give the mother supplements, which we have done, and do that sort of randomization. There is a general laziness that I find in nutrition research, where people say you can’t do that because this is nutrition, it has to be an open study, and then you end up with the sort of data that you are talking about. Finally, you have highlighted the very real gap that’s opening up between the clinician and the scientist, and we’ve had a hard time trying to attract clinicians into our projects for the very reasons that you have outlined. I know that clinicians who are actively working in research have the same trouble attracting scientists, but the marriage is absolutely essential, that we have both arms going, and I always despair when I start hearing about research institutes wanting their own buildings; I want to see them embedded in hospitals where you can see where the need is.

Dr. Spieldenner: Taking the role of a policy advisor, I would be puzzled after the last two presentations as hardly any recommendations and guidelines got through to those who have to implement them, that the research done in the last 20 years did not lead to any real innovation and that not enough money was put into this field. In conclusion, it would be hard for a policy advisor to recommend to put resources into a science that does not create real innovation and communicate its results to the people.

Dr. Bier: I think that we have done a little bit of that. Frankly, I think it’s potentially important to have these micro-manipulations of infant formulas and all of that sort of stuff, but that’s not going to drive the cutting edge of pediatric research. Several people in this room are doing longitudinal studies which will give us answers to things that will happen over time, but we are left with all sorts of hypotheses in pediatrics for which there are no hard end point variables. We now have the whole issue of developmental programming, where we had initially no clearly plausible mechanistic data. Then, in animals we got a variety of really good mechanistic data that have you believing that these things are possible. Now we have to determine whether these mechanisms apply in humans. But how are we going to do those experiments? We are not going to find out by association.

Dr. Solomons: You have made some both on the record/off the record comments about the certainty of findings which has to do with reproducibility that are provocative, and as a matter of fact I very much support that statement. However, I want to question the motivations and the reward system that we have. Publishing the same findings twice has certain probabilities in the reward system we use for publications, so if we use the standard it should be published twice, the first time was outstanding news and discoveries, but who is going to publish the paper the second time, especially if it’s a negative finding on both occasions? That’s the publication issue, where will we find that mechanism for the reproducibility that adds the confirmation that needs us to go forward.

Dr. Bier: I think it depends on the nature of the question and how important the answer is to society. Some of the negative homocysteine trials were published in The New England Journal of Medicine, JAMA. Reproducibility of a relatively minor observation may be important ultimately to science so that we know it, but that is not going to necessarily compel getting the second paper published. However, there are lots of observations that are so important to human society or nutrition or health that they will.

Dr. Solomons: Let’s go to the second part, which has to do with motivation for how we give rewards both in commercial innovation, industry let’s say, and how we
give rewards in what you and I do, which is academics, and there we have your recommendations for science which costs more than the aggregate NIH for instrumentation. That’s where I think it runs into big trouble. We need to have the investment from capitalism’s wealth and a socialist ethos for the distribution of its access. I am often frustrated with my close friends from one industry or another who say we have got to get more market share rather than their collaborating with their resources to something which I think is compelling. The academic side has to do with asking the question that gets you promotion, recognition and otherwise, and sometimes the question is tied to the use of, for example, the MRI. My suggestion there, the socialist ethos, is that if there are people in Bangladesh or Philippines who have a compelling question and you have the MRI, what’s the access of their to use it since it is a very expensive apparatus that could be very useful when they’ve come across the compelling question but certainly could not have the access to this technology?

Dr. Bier: If the study can be done by having samples of something run in the US, I say that there is access. Having run resources where we have people from all over the world using these things, I don’t think that’s an issue. Again, the people who run the resources are interested in the quality of the question. They get requests all the time to use their instruments, and they say ‘why do I want to use it for this, this isn’t worth the answer’. If the answer is worth it, people find a way to do the samples. But there are a lot of MRI studies where you have to find a way to get the instrumentation and the resources in the place where the study can be done. Most big medical schools realize that having instrument resources brings in grant money. Bringing grant money pays salaries, pays overhead. The more grants you have, irrespective of what else you do for the university, that makes university happy, they build the resources. It’s not any different than other kinds of businesses.

Dr. Cooper: Certainly, part of the problem is almost a complete lack of funding within countries for research in many developing countries. Speaking from South Africa which is, I think, by far the best resourced country in sub-Saharan Africa, the amount of funding we can get from our equivalent of the NIH is absolute peanuts. To do proper research, it has really become necessary to depend on collaboration with funders from outside of the country and from the developed countries, and only a few researchers have really got to the point where their research profile is good enough to be able to attract that sort of funding. Although we have been talking about whether the study done in North America is applicable to China and so on, my experience in a fairly multiethnic country is that there are far more similarities than differences. Therefore, I would urge people in this room and beyond to look for partners in developing countries because I think there are very important questions that can be asked in those countries that will still have major relevance to all parts of the world.

Dr. Bier: I think that it works both ways though. I think that many investigators in the US would not be aware that there is a population available in a developing country that would answer a question that might interest them. They are generally not going to go out searching, but suppose that there is a unique set of populations and nutritional circumstances in South Africa that will tell us for sure the answer to X or Y. Bring that to the people who may be interested in the answer, it works both ways.

Dr. Lönnerdal: I would like to bring up one issue which I am sure you are aware of but I would like to emphasize here since we have been talking about the age period of 0–6 months. I have been on NIH grant review panels, program project reviews, the USDA human nutrient requirements grant panel, etc., and it is very difficult to get any funding for that age bracket because in most of the studies what we would like to compare is breastfeeding, which has basically no commercial interest behind it, and the alternative is formula feeding, and that is of commercial interest. Therefore, colleagues of mine on all these review panels basically would downgrade the priority and
say this should be funded by the formula industry. So very little of this funding would
go to that particular age bracket. I think that in the US one of the dilemmas is that we
don't yet have these partnerships that we see in some of the European Community
countries, and in Australia. There, you have partnerships between industry and non-
profit organizations or governmental institutions. I think we need larger initiatives and
better funding to do this.

*Dr. Bier:* There are areas of all sciences that are harder or less hard to get funded.
In the case of those issues, it's a question of how important the answer is that we need
to know, that we need to spend the money on, and that's a value judgment by the
people who give out the money.