Bioethics and Innovation in Pediatric Nutrition Research

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Abstract
Advances in technology and understanding of fundamental human biology allow for an increasingly innovative research agenda in pediatric nutrition. All human research is governed by the norms of bioethics, which are in turn based on four primary principles: free will in participation, freedom from harm, opportunity to benefit, and non-discrimination in access. Legally, if not essentially, juveniles do not have free will to affirm their participation as research subjects. They have an absolute right, in nontherapeutic research, however, to decline. Pivotal in the discussion in nontherapeutic research in healthy children is the tolerance for risky procedures. Complicated situations include: multi-national protocols, choice of developing country sites, the inclusion of placebo treatment arms, analysis of genetic biomarkers, and research for commercial enterprises. The overly stringent interpretation of bioethical principles, as adapted to children, would stifle innovation in research. A relaxed bioethical attitude in pursuit of advancing science, by contrast, could violate essential human rights and expose a population worthy of special protection to undue risk and harm. By following the course of utility, seeking the steepest benefit-to-risk ratios, weighted toward safety and child welfare, the divergent nature of the considerations should be brought into convergence for the sake of continuing innovation.

When you reach the fork in the road, take it.
G.T. Keusch [1]

We live in a world of growing population, shrinking natural resources, a stable – but precarious – food supply, unstable climate, and differentially shifting demographics in developed and developing countries. The current world population is estimated to be 6.8 billion, with 27% under 15 years of age, and 10% below 5 years. Pediatric nutrition research could potentially affect the lives of billions of individuals.
Today, we also have unprecedented communication capacity, with interconnection among all regions and societies of the world derived from rapid air travel, massive oceanic shipping and trade capacity, informatics, and a shift away from the regional hegemonies of the Cold War era. The situation is a two-edged sword. It brings awareness of ideas and norms from one part of the world to another, but these may clash with the values in the other part. Moreover, despite our means and media to communicate, the degree of understanding and trust across regions and cultures, across nations within regions, and among classes within societies, may actually be in retreat.

Values, Morals, and Ethics: The Governing Principles of the Social Compact

Values, morals and ethics are elements of the social compact that holds societies together and allows for cordial and just relations among the members. Despite the semantic confusion and recognized interrelationships, the three terms are not synonyms and must be understood in their appropriate connotations and contexts.

The Definitions and Distinctions

The definitions of the terms of reference are provided in the upper panel of table 1. In the broadest sense, each deals with good and bad, right and wrong. Social values are collective judgments as to what is important to and in a
society. What is appropriate interpersonal behavior derives from these judgments. Therefore, what constitutes ‘good’ and ‘bad’ treatment of one’s fellow man or woman is based on the values adopted in the society. Morals are the values that directly express right and wrong. Morality constitutes the convictions that are held to be authoritative in matters of right and wrong. Ethics is a code of conduct for approved relations among persons, one that is dictated by the social norms of the society.

The Ethical Principles of Bioethics

Biological and medical sciences represent professions in which an ethical code is an obvious necessity. Biomedical ethics or bioethics is the domain of the ethical code of conduct in issues of medical practice or research. The four hallmark principles of bioethics are: autonomy, nonmaleficence, beneficence and justice; they are defined in the lower panel of table 1, and have been expanded upon elsewhere [2, 3]. The basic general principles and considerations of bioethics have contributed directly to the formulation of treatises dealing with diagnostic and therapeutic issues in the clinical context [4], preventive issues of the public health [2, 5, 6], and investigations involving human subjects [7].

According to Graber [8], ethical theory has two tasks: ‘(1) for those situations in which we already know what is right and what is wrong, it should help us explain why the one choice is right, and the other wrong; (2) for those situations in which it is not obvious, what is right and what is wrong, it should guide us to discover what is the right thing to do’. For instance, the principles of beneficence and nonmaleficence could be seen in absolutist terms, such that neither can be violated. This is akin to requiring all diagnostic screening tests to be both 100% sensitive and 100% specific at the same time. The probability of perfection for either situation is remote. Thus, we are inevitably faced with ethical dilemmas, and the issue of finding an acceptable balance. The exigency of dilemmas has given rise to a (relativistic) fifth principle, which is not ranked among the big four, but is importantly operative for the present discussion. This refers to what Beauchamp and Childress [3] call the principle of utility, which emphasizes the ‘benefit-to-risk’ ratio as the final governing arbiter in bioethical dilemmas at the interface of benefiting the participants and doing them no harm.

The Bioethical Principles Applied to Biomedical Research

The original motivation for concern about human investigation was moral and ethical atrocities committed by the Axis allies during World War II, and later uncovered in US institutions. Table 2 provides a chronology of important historical landmarks in research bioethics. As of 1978 in the US, a legal framework of regulation of human research has been codified. Among its requirements is the approval and supervision of studies on human subjects by oversight bodies known variously as institutional review boards, and independent ethics committees or ethical review boards. These are to assure protection of subjects’
Table 2. Important landmark documents and declarations in the history of the ethical protection of human subjects in research

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<th>General and universal statements</th>
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welfare and ethical conduct of human research, including respect for autonomy with informed consent for individual participation. As an example from North America, the fundamental elements of informed consent under US Federal regulations [9] are outlined in table 3. Specific bioethical regulations regarding supervision of human investigation vary from nation to nation.

Social Values and Innovation in Investigation in Children

The theme term of our workshop, ‘innovation’, can be defined as the process of introducing something new. It has multiple and interacting connotations in the context of bioethics and pediatric nutritional investigation. The first is the wide gamut of emerging and novel research questions surrounding diet, nutrition and physical activity, which represent innovative inquiry. The
Table 3. A description of the elements of informed consent for participation in medical and health investigations according to the US Federal Regulations Codes

1 A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental
2 A description of any reasonably foreseeable risks or discomforts to the subject
3 A description of any benefits to the subject or to others which may reasonably be expected from the research
4 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
5 A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
6 For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained
7 An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject
8 A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

From Title 45 Public Welfare [9].

challenge for safety and efficacy – but more for containment of health costs – brought the term ‘evidence-based’ practice into vogue at the close of the 20th century. The best investment in health and nutrition for the individual citizen’s money or with the public funds was seen to be the one demonstrated by rigorous scientific evidence. To the extent these inquiries respond to the needs of the world’s juvenile population and provide solutions to problems, they are essential.

At least in Guatemala, a more colloquial connation comes from the National Council on Science and Technology (CONCYT) of Guatemala which sees its mission in the promotion of Research, Technology and Innovation in the national interest; for them, the latter term signifies applications that can be patented or turned to restricted uses in a commercial sense, eventually to contribute revenue.

Social values and financial prowess influence the pediatric research agenda, and this lies upstream of the research ethics. Regarding innovation in complementary feeding and its timing, for example, the World Breastfeeding Alliance (WABA) laments that ‘amongst the many stakeholders in malnutrition, there is no well-resourced breastfeeding champion’ [10]. As a consequence, public-
private funders ignore indigenous, traditional complementary feeding options. An informal international consortium of public health nutrition investigators, the Child Health and Nutrition Research Initiative (CHNRI), performed a unique triple survey among diverse stakeholders in health research and their representatives. Two were conducted in an international context and one within the confines of South Africa [11]. The queries related to prioritizing five basic considerations in research planning. The phrasing in one of the questionnaires is show as an example in table 4. CHNRI found: ‘At the global level, the wide and diverse group of respondents placed the greatest importance (weight) to the criterion of maximum potential for disease burden reduction, while the most stringent threshold was placed on the criterion of answerability in an ethical way’ [11]. By contrast, those surveyed in South Africa found the predicted impact on equity to be the most important. These researchers argue for the ideal of a broader consultation on setting research priorities, beyond the investigators themselves.

Prof. Jerry Keusch, renowned leader in Global Health, has developed an evolutionary argument in his publication ‘When you reach the fork in the road, take it: science and product development as linked paths’ [1]. For him, scientific inquiry has emerged from the pure animus to know how nature operates, through the obligation to publish and disseminate new knowledge, to a contemporary imperative to make applied use of the findings. His new motto for scientific inquiry becomes: ‘if it is not used, it is not done’. He focuses on research education and career development as an often ignored element in the discussion. Keusch’s synthesis is a convoluted and interactive one. He argues that the: ‘education and research system must ensure that the scientific workforce will understand public needs, that the public health workforce will understand the contributions of science, and that the financial and organizational mechanisms that create the private good of products for better health care can address the global public health requirements for global

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**Table 4.** Five considerations related to priorities for research investment in the basic questionnaire of the CHIRI survey series

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<td>That the new or improved health intervention is likely to indeed be developed through proposed research investment</td>
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<tr>
<td>That, if developed, it is likely to have a real and true effect against the disease it aims to tackle</td>
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<tr>
<td>That, if developed, it is likely to be delivered to most of those who are in need for it</td>
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<tr>
<td>That, if developed, it is likely to influence the majority of affected individuals</td>
</tr>
<tr>
<td>That, if developed, it is likely to become available to all segments of the society equally</td>
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development’ [10]. In light of such contrasting – if conflicting – social values considerations, there may be need for finding innovative application of ethical theory to inform us about the ethical dilemmas that the innovation in the research agenda generates.

**The Constraints of Assent, Risk and Child Welfare in Pediatric Research: The Judgments in the Ethicists’ Literature**

The four bioethical principles are operative in pediatric research, but the tender age of the population brings out three correlative issues: power relations, informed consent and confidentiality [12]. There is an extensive debate in the pediatrics literature over the meaning and application of autonomy for children’s participation in research. The law generally sees minors as legally incapable of giving consent. As the wards of parents and guardians, the responsible adults must provide the informed consent (or, in effect, ‘permission’ for participation) or not. However, there is a requirement for the child subject’s ‘assent’. Maturation of decision-making among adolescents is heterogeneous, but one noted ethicist suggests that 14 years is an age one when ‘become(s) able to understand the research in question’ [13]. There is general consensus, however, that respect for a child to dissent (refuse participation even if parents have consented) should be absolute. The current fulcrum of controversy is whether parents and the law should respect the positive assent decision of a child, short of legal age of maturity [14]. Adult guardians, however, can sign their children up for investigations that are unsafe or harmful. One reaches the conclusion that autonomy and nonmaleficence are more intimately intertwined for this group, since, no matter who makes the positive decision for a child’s participation in research, the protection from harm for this vulnerable population emerges as paramount.

Despite the nuances, as stated by many commentators, it is unethical *not* to involve children in investigative research. To the extent that drug efficacy for children is generally extrapolated from adult experience, the US government has encouraged the conduct of ethical drug trials in and for children [15, 16]. Drug studies are the point of departure for discussion of beneficence and justice by Rowell and Zlotkin [17]. They call above all for the mobilization of advocates for the children’s well-being, while finding merit in empowering children, without discrimination, to safely ensure that medications are secure and effective for pediatric use.

**The Geographic and Cultural Encounters**

Multinational research in pediatric nutrition is clearly one of the avenues of innovation, since resources and technology in one location must
be merged with the existence of the problem in another. Here, issues of relative power and sophistication merge with those of cultural values and national sovereignty. At one level are arrangements within a single region, such as the EU. Indeed, there have been murmurings from British professionals about loss of UK ethics sovereignty from EU-wide directives. In actuality, the collaborators in the Healthy Lifestyle by Nutrition in Europe in Adolescence (HELENA) Study [18], which involved European children (adolescents), documented the diverse and persistent efforts needed to achieve all of the legal and ethical board approvals across the ten nations of the network, with all of their different norms and the different considerations raised. The optimistic moral of their tale is, however, that it proved able to be done [18].

North–South collaborations in research financing and investigation raise both similar and different issues. If indeed there is mistrust across the English Channel and inconsistency with the EU, the bases for mistrust and power differentials with affluent collaborators joining with colleagues in middle- and low-income countries are more profound. As related by Pitler [19], one of the legendary international clashes of culture related to the inclusion of a placebo arm in a study of prevention of maternal to child transmission of HIV, in which the editor of the *New England Journal of Medicine*, the venue of publication, took the ethics of such a design to task in a stinging Editorial, alleging that the participants should be offered ‘state-of-the-art’ treatment. She meant state-of-the-art for the US, the funding nation. A counter argument relates to the sustainability of the most advanced therapy if declared a standard of care in a resource-poor country. Innovation requires both the most advanced – but also the most practical and appropriate – technology when resolving problems in low-income settings.

Hyder et al. [20] openly recognize the diverse weaknesses and limitations for conducting ethical research in less-developed societies, and propose a solution in a *Lancet* review entitled: ‘Moving from research ethics review to research ethics systems in low-income and middle-income countries’. This system approach looks to deepen the bases for an ethical research environment through issues of: development, enabling conditions, national/regional strategy, institutional commitment, and investigators’ conduct, in addition to the research ethics review process itself. It is pertinent to consider their entire treatise, but just the list of the ‘enabling conditions’ considered by Hyder et al. [20] is highly illustrative. These conditions include: values, strong civil society, cadres of trained people, healthy working population, public accountability, trust in basic transactional processes, and freedom of people to determine boundaries of personal risk. These requisites set the bar high, with criteria that would be utopian even for the most advanced societies. They inform and guide emerging societies, while raising the question of how ethical research can be conducted in the countries of the South before the consolidation of the ethical system conditions.
Ethical Flash Points in Pediatric Research

Beyond the training, infrastructure and commitment to protection of subjects, are a host of sensitive ‘flash points’ of ethical dilemmas in the design of some of the most innovative and high-value research. Among the points of contention are the enrollment of children for nontherapeutic inquiry with no direct benefits, the inclusion of placebo (nonintervention) controls in the research protocol, and the obtaining and divulging of genetic information gathered in pediatric research.

The Role of Children in Nontherapeutic Research

There are more ethical certainties in research on children affected with a disease or condition, as they might benefit directly from a successful new therapeutic approach; this is in contrast to research in healthy children with no major benefits to be reaped. The degree of risk in the privations, exposures or procedures acceptable in this population needs to be better understood. In the US, Federal regulations call for no more than ‘minimal risk’ in child research, or alternatively ‘no more than a minor increase over minimal risk’. Fisher et al. [21] identified: ‘the ethical issues posed by ambiguities in regulatory language’, and call for ‘a national consensus on recommended criteria’. Ross [22] calls the current language a ‘double standard’ and calls for the unification of criteria. Failure to arrive at a robust resolution of nontherapeutic research dilemma regarding ‘risk’ threatens innovation research for preventive nutrition.

The Role of Placebos in Controlling for Positive and Negative Effects of Intervention Studies in Children

As discussed, the use of placebos is controversial in HIV research [20]. In pediatric research, this has extended over into relatively benign conditions, such as mild hypertension, in which a controversy concerning leaving children untreated for even a short period has been debated [23]. US Federal regulations permit placebos in pediatric clinical trial protocols under stringent conditions, but again related to the ambiguous ‘minimal’ and ‘no more than a minor increase over minimal’ risk criteria [24]. For healthy children and nontherapeutic research, the US government is somewhat ‘agnostic’ on the subject of placebos.

In childhood nutrition, addressing endemic nutrient deficiencies and imbalances sets the scene for a dispute over placebo-containing study designs. In situations in which spontaneous improvement of a condition or developmental changes with age, such as hematological status, it is difficult to discern what effects on anemia prevalence could be attributable to an iron intervention without a situation of control reference. On the safety side of the ledger, there are examples in which interventions were found not only to be nonefficacious but even to be harmful, but only by virtue of a no-treat-
ment arm included in the design [25]. Safety is a higher essential priority than efficacy for nutrition innovations. Appropriate control comparisons are indispensable for detecting any adverse effects or damage in intervention research.

Collection of Genetic Information in Children

The issues of nontherapeutic research and placebo interventions in healthy children are not the only sensitive issue in pediatric nutrition research. An even more sensitive issue surrounds obtaining consent for and maintaining anonymity of identification in the collection of genetic information in children [27, 28]. When it comes to screening for genes associated with adult-onset disease, for example, it was a consensus that: ‘If there were no urgent medical reasons, all guidelines recommend postponing testing until the child could consent to testing as a competent adolescent or as an adult’ [27]. Writing from Malawi, Ndebele and Musesengwa [28] fret, beyond resolution of the ethical pitfalls, about what tangible fruits application of genetic techniques might hold for developing countries; their perspective and concerns deserve serious consideration.

One of the recognized foibles of randomized clinical trials is that they involved representative – but unselected – populations, in which the vulnerability to disease development and susceptibility to benefit are heterogeneous and not synonymous [29]. A more valid test of efficacy would come from enrolling and randomization only of those with susceptibility to an affliction, if this could be identified. Conversely, universal en masse application of preventive measures will have uneven and inefficient effects if the exposed individuals do not all have a substantial chance to receive benefit from the efforts. As far back as the 1980s, Holtzman [30] argued to the nutrition community that ‘selective policies should be considered when discernible differences in risk exist...’ Within today’s armamentarium of genetic biomarkers, a contorted interface of innovation and ethical complexity arises in the domain of pediatric genetics and genomics research. Hang-ups on the ethical dilemmas surrounding genetic profiling of minors could seriously stifle innovation in preventive nutrition.

The Footprint of the Investigative Enterprise on Participating Communities

Not on the flash point list, but important for those of us who live in low- and middle-income countries, is the issue of the ‘footprint’ a research study may leave in the participating communities. What we call ‘developing’ societies are, by definition, susceptible to rapid evolution and change. Inducing changes in behavior, for the purposes of a research investigation, may contribute to social evolution and change with unintended consequences.
A pivotal point in ethical theory for innovation research is around the issues of how to restore the participating individuals and families to their prestudy community norms if the tested intervention proves to be either inefficacious, unsafe or both. In a Guatemalan case in point, a permanent loss of ‘market share’ for agriculturists who were retired from the maize commerce to participate in an improved corn variety intervention became a concern [31]. There is the related concern of avoiding ‘contamination’ of the traditional behaviors among nonparticipant neighbors who might mimic or emulate a course advocated by the investigators to the selected few enrolled in a study.

Finally, the scope of the beneficence principle intercedes with respect to sustaining any beneficial effects found in a study. How are they continued in the treatment arm sample, and for how long? When and how are they extended to the control group, who did not benefit during the trial? What is the obligation to bring the benefit to the community as a whole? The region? The nation? Often, the low-income country values and policies feel that sustained subsidizing of the benefit, with funds from the investigation, is a moral obligation of involving the population in the research. The other side of this coin would be any obligation for compensation to families, community, etc., for adverse effects discovered during interim data monitoring or at the conclusion of a full intervention trial, as exemplified in the Pemba study [32, 33] (box 1).

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**Box 1**

**Case study**
Effects of Routine Iron Supplementation on Anemia and Health of Children in a Malaria Area in Tanzania

A consultancy conducted in 1998 by the World Health Organization (WHO) and the International Nutritional Anemia Consultative Group concluded that, when the population of children aged 6–24 months in a given locality had an anemia prevalence of >40%, universal supplementation of the target group with 12.5 mg of iron and 25 µg of folic acid should be instituted as a public health measure [32]. In an area holoendemic for malaria on Pemba in the Zanzibar Islands of Tanzania, involving 24,076 children, randomized to iron, folic acid and zinc, iron and folic acid, zinc alone, and no-treatment (placebo) [33], an interim analysis by the Data Safety Monitoring Board detected a trend towards increased adverse outcomes in the groups randomized to iron, as compared to a placebo (no treatment group). The iron supplementation intervention was suspended. A formal analysis of the accumulated findings before cessation of the iron trial found a 15% increased risk of death, an 11% increased risk of hospitalization (statistically significant, p = 0.03), and a 12% increased risk between the combined adverse outcomes (statistically significant, p = 0.02). A consultancy group, convened by the WHO in Lyon, France, subsequently recommended a moratorium on universal iron interventions in malaria holoendemic areas.
Conclusions

The imperative for innovation research is driven by the interests of those who can benefit from the new knowledge and its application. At times, the dilemma can be posed as a conflict between the compromise of the welfare of the young individuals, who are enrolled or otherwise included, and the greater good for their peers in society. Ethical quandaries can prove to be a damper to innovation at one level and a stimulus to innovation at another. A case study summary of the now notorious iron supplementation innovation in a high-incidence malarial population [33] is presented in box 1. The international reaction to the occurrence was a recoiling and retreat from universal iron supplementation for children in such areas. However, it has also stimulated the quest for innovations to overcome the barriers. This includes such ideas as noninvasive (bloodless) screening of hematological and iron status to target therapy to the truly deficient or develop alternative ways of providing iron with compounds less provocative of adverse outcomes [34].

The advance in scientific knowledge and applicable technology in basic laboratory science is inexorable. It will be funded by public funds and corporate investment. By limiting the application in children, bioethical principles may appear at times to stifle innovation in pediatric nutrition. The prospects for certain lines of pediatric research will inevitably come to forks in the road [1]. By following the course of utility [3] to seek the steepest benefit-to-risk ratios [17] with a profound weighting toward safety and child welfare while always respecting an absolute right to subjects’ dissent [13], the divergent nature of the considerations should be able to be brought into convergence for the sake of continuing innovation.

References


Discussion

Dr. Gibson: I personally have never been restricted in any of our research in terms of ethics. Everyone that I know who conducts ethical research sits quite comfortably within the context of the ethical rules in our hospital, and further we ask ourselves another question: would I let this be done to my child, and that's a question we have asked ourselves repeatedly and then turned our backs on some tests. The thing that really bedevils us is one of the steps that you brought forward, and that is what I would call the translation. The public gives us enormous amounts of money, we do these studies, and then it sits comfortably on somebody's shelf I don't know how long. Then it gets published in JAMA or BMJ or any other journal, and it just sits there unless there is some organism that has got the money, the energy and the time to see that the findings are translated either into a product on a supermarket shelf or in clinical practice guidelines or a number of other things. We need creation of translation mechanisms, I am a nutritionist, somebody else is a translational person, and unless they pick it up and provide dollars nothing happens, I think it's almost immoral, and it's certainly frustrating.

Dr. Solomons: I think it's moral. I've often said to my post-docs and graduate students it's immoral for you not to get that paper off to the journal, whether it was a negative or a positive study. I have a very close friend at Stanford University, who said that there's an intersection between health care efficacy and its just distribution in society, and he said: here's where I take off, I make sure the studies are as good as possible, and when they show a significant benefit, it's my job to find out how we move that translation from a significant benefit demonstrated to those who need it as quickly as possible. Yesterday we had a discussion about the issue of meta-analysis, size effects 11% significant, 20% significant. I was cheering all over the place because I think 18 lives saved out of a 100 is a significant issue. But there are some people who operate from an abundance of caution and clamor to see a study redone and confirmed and viewed in the context of meta-analysis; this is an overabundance of caution perhaps. What happens in our ethics, and I think you have probably seen this, is that once an intervention measure has a powerful lobby behind its efficacy it’s no longer ethically acceptable to use a placebo, so we can't really confirm it. This is another argument to design it right the first time because if you get a sort of a rumor out there and the rumor is wrong but placebo research is constrained for ever, you have done the worst of all evil to the situation. That’s my response to that. Really get it right the first time, because once the moral ethicist will say ‘no longer placebo here’, the repeat study is totally proscribed from ever being done.

Dr. Cooper: I just have to take you up further on that. I think the end points become very important and particularly looking at the nitric oxide study that in itself I think was a very good study, but going back a little further in the neonatal research steroids given to premature babies to either prevent or modify the development of chronic lung disease came in a very few relatively small studies, became very widely used, and it took probably more than a decade to realize that it was having harmful long-term effects in terms of an increase in the rate of cerebral palsy. So, I think if we go back to Dr. Makrides’ studies, a 7-year follow-up, is clearly very important, and a longer follow-up is necessary to be sure that there are no long-term harmful effects, and I think that's where the importance of publication, discussion, presentation at meetings becomes very important to explore these areas.

Dr. Solomons: Let me mention just two key words, thalidomide and ethylstilbestrol. That's an intrinsic and sad aspect of research, that is, that it is always easier to develop an efficacy statistical profile faster and with a smaller sample size than to see the long-term safety. So, in fact ethylstilbestrol did preserve fetal implantation and
allowed for birth. It did it very powerfully. It was only later, 20 years later, that vaginal malignancy was found to be an awful consequence. Thalidomide was a little closer, it did provide sleep and antinausea for women who were pregnant, but at the same time, it did produce children without limbs. It takes a while from efficacy to safety because safety requires a much larger sample size than efficacy.

**Dr. Cooper:** I think one of your last slides was on profit, public good versus private profit. I think there the dividing line is not clear at all. As an example, one of the major studies on pneumococcal vaccine was done in Soweto in South Africa. At the time, I was in the ethics committee, and one of the questions asked was this is never going to be affordable in the countries where it matters most. Yet, the study went ahead, and we have seen major changes in global players such as the Gates Foundation, and now it is becoming available very widely in the poorest of countries. So what might have been going to benefit the company 15 years ago has now become an enormous benefit to the whole population of children worldwide.

**Dr. Solomons:** That's a wonderful case study, and I think you are right, the same thing happened with antiretroviruses.

**Dr. Ruemmele:** I completely agree with what you've mentioned, that children are particularly vulnerable and have to be protected, so there are major issues and controls if you want to perform trials in children, mainly drug trials. But now I think the picture is moving on because in pediatrics we have to treat diseases and a lot of drugs we use for various indications are off label, there is no approval, they are not tested. The agencies in North America and in Europe now urge us to do these trials, so I think this overprotection of children is now moving to 'now you have to test and to reassure that what you've been doing over the years is appropriate'.

**Dr. Solomons:** They started saying that in 1991.

**Dr. Ruemmele:** Yes, but my feeling is that protection of children limits a little bit very useful and beneficial research with this regard. What is your comment on that?

**Dr. Solomons:** My comment is what I commented during the talk: that there are some situations in innovation in which the ethical practices would be road blocks and will act as road blocks. My answer to the question is that there are ways through it in an ethical manner, I rely back on Graber and ethical theory, it's a very positive aspect that if you understand it and talk it through you can come to a decision which moves things forward, even for children.

**Dr. Bier:** As far as the pharmacologic studies are concerned, in pediatrics there is a pediatric pharmacological research unit network which exists throughout the major medical schools. We do some very large number of pharmacologic studies in children precisely for this reason. In fact, it was a government priority and they established the units for that purpose. These are studies in which there is an indication of the drug.

**Dr. Solomons:** That's right, that's a step up. As you know, safety studies in adults for drugs start with safety studies, and I submit that during that kind of safety study just finding some healthy kids to see if anything goes wrong is not done, cannot be done, should not be done.

**Dr. Bier:** As you pointed out in your talk, there is essentially no way to prove safety except from massive numbers and long experience, so small studies for safety don't work.

**Dr. Solomons:** But we do large studies for safety in adults, that's the point.

**Dr. Ivarsson:** I agree that publishing research findings is crucial; however, our responsibility doesn't end there. In my opinion, we as researchers also have a responsibility to explain the findings in a way that makes them understandable and useful for the society. If the findings are from pharmaceutical research, the drug companies support this process. However, in the field of public health, for example, with respect to the need
for behavioral changes in the population, there is not a strong driving force that sup-
ports the move from evidence to practice. Do you have any comment about this?

**Dr. Solomons:** It’s much more likely that a promising finding that was financed
by industry money and is patented and has intellectual property rights is going to be
used, not necessarily gain access to those most needing, than something which comes
out of the public domain. Now, I have two men both of whom I know both well, one
has recently deceased, Guillermo Arroyave of Guatemala and Al Sommer, both who
worked in vitamin A, and both who found, reported and published important interven-
tions that were successful against vitamin A deficiency. Dr. Arroyave was in Guatemala
and did the studies in Guatemala, he published the studies in *The American Journal
of Clinical Nutrition*, and then the government of Guatemala would not move. So
what he did, he took the blind children from the school for the blind into the galleries
of the legislature on the day they were going to vote on it, and it passed. But he took
that initiative in conjunction with the woman who ran the school for the blind; he used
some guerrilla theater and he got it across. I often criticized that, I said there should
be a non-me (external) evaluation of what I publish to translate it. Now, let’s move to
Al Sommer who had a bigger study with bigger findings (34% reduction in mortality),
in a bigger population (the whole island of Sumatra). He went to the US Congress
and received financial support to do what you now see as vitamin A supplementa-
tion all over the world for prevention of child death. If we are looking now, as every
intervention seems to weaken over time, there may have been too much of an ‘I am
the investigator, I have to be the advocate’ attitude in both instances. There needs to
be break on direct transfer to policy and program and translators between the finder
and that person’s own advocacy. I am inclined to think that there should be an agency
somewhere upon which investigators can call for translators who can make external
and independent judgments.

**Dr. B. Koletzko:** You as well as Dr. Cooper discussed potential conflicts between
private companies and public agencies regarding values or priorities. Is there not a
potential problem sometimes with public agencies as well? The design of clinical tri-
als on drugs and on pediatric nutrition products is often very much influenced by the
requirements for registration of products or ingredients. There are many examples
where these requirements formulated by public agencies are not at all shared by the
scientific community. For example, oftentimes growth studies or absorption studies
with balance studies are requested where most experts in the field would say: ‘We
really don’t have a reasonable hypothesis on which to base that requirement. Why
should we burden infants with such absorption studies?’ There are other examples
where studies are requested to be repeated merely in a different country, to show
results in the country where a product should be registered. Even the US are not an
exception to that concept. Is that not also a concern?

**Dr. Solomons:** Yes, but that’s a complex question. I am glad you mentioned Dr.
Cooper and me in the same place because while I was praising the organizers of this
meeting initially for all the bilingual, multilingual people around the table, all the glo-
balization in the room, I also want to point out that there are only two people among
the speakers who are from countries other than the countries of the North. Dr. B.
Koletzko is not responsible for the distribution of published research on fetal pro-
gramming at the moment, you are not, but I think you should be part of an advocacy
to see that resources have flowed in some way to the better researchers in *developing*
countries. In this way, Denmark, UK, Germany, etc. would not be the only countries
having invited speakers. So I think there is a justice issue. Yesterday, Dr. Spieldenner
said something wonderful, he said that in any given year 7% of the Chinese popula-
tion of children constitutes the number born in all of the European states. So, why
is Europe getting more investment? They have more money to start with to invest
among themselves, they have better researchers. So justice, which I made the center piece of my talk, begins to respond to all the parsing of your statements. Now, what we have surpassed is the attitude ‘let’s go to a poor country because it has a lesser ethical regulation and we can do something there we can’t do here’, we have gone beyond that. The most interesting one, ‘we have papilloma in Soweto, we have papilloma in Paris, and we do the papilloma research in Soweto to get rid of the papilloma in Paris’, we are getting beyond that as well. So once you've identified the dilemma, you talk honestly and openly about it, you point it out to try to find a way forward. I think we are doing well. Most people are not complaining about the way ethics works. I think there is a tremendous positive feeling among these stakeholders that basically we are trying to do ethical good work and that we basically succeed more often than getting meta-analysis in order.

Dr. Haschke: One comment on the South-African situation and the antiretroviral drugs. It was not the issue of knocking at the door of pharma companies to get the drug. After it had been realized that the drugs are efficient, it was in the 1990s, of course the pharma companies tried to sell them in the southern part of Africa at prices which were not affordable. What was then done, generic drugs were imported from India, and they bypassed all the license fees. I remember quite well in 2001, at the World Health Economic Forum in Durban the heads of states met the heads of the companies. There was agreement that there would be some substantial decrease in the license fees, making all these drugs available to the population. What was done, the political leadership of South Africa denied the efficacy of these measures until 2005, and the population suffered from this. In South Africa the issue is very complex, it’s not related to intellectual property on the one side and to not having access to the drug on the other, it’s more complex, politics here played a very negative role.

Dr. Solomons: I will accept that history because I did know the former Minister of Health of South Africa, but I think that you overcomplicated the ethical point about when there is no access. The ethical point is when there is no access to those who most need it because of intellectual property times market price. I think what you are saying is that you also, given the position you have in industry, are in favor of generic non-license copying, pirating if you will, bring on the pirate competition and we won’t sue in the Hague, we will just applaud the initiative of bringing it to the people who need it. Am I interpreting you right?

Dr. Haschke: I am not giving you a legal view because I am not allowed to do this, but negotiations in that case are the best thing you can do with the companies. The companies showed the understanding of what the situation was, they realized what had happened, and they found an agreement; this was finally the best way to go.