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Reflections on Future Research in Adolescent Reproductive Health

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Abstract

A group of basic scientists, clinicians, clinical investigators, psychologists, patient advocacy groups, and representatives from professional societies and governmental agencies met at the National Institutes of Health in October, 2007 with the long-term goal of having the menstrual cycle accepted and understood as a marker of general health in adolescent girls. An equally important goal was to develop a research agenda for this area of investigation. This chapter comprises the highlights of discussions throughout that meeting, with an emphasis on ideas generated during a final session led by an internationally renowned physician-scientist, in which reports from four breakout groups were presented. The specific goal assigned to each group was to develop an agenda that would set the stage for how research should be conducted over the next 100 years, and to identify the pressing research questions that should be addressed related to the menstrual cycle and adolescent health. The four areas represented in discussion groups included: genetic research; metabolic and reproductive research; emotional health; and the promotion of conduct of clinical research. Insights are also provided by five clinical investigators, including two outside experts, on both topics of priority for a research agenda in the area of adolescent reproductive health, as well as how the research itself should be conducted.

Keywords

research; adolescents; reproductive health; menstrual cycle

Background

Individuals from diverse backgrounds, including clinicians, clinical investigators, basic scientists, psychologists, patient advocacy groups, and representatives from professional societies and governmental agencies convened at the National Institutes of Health (NIH) for a meeting to discuss issues relevant to "The Menstrual Cycle and Adolescent Health." A research agenda was also generated which covered topics of priority in this area for the next century. A goal of the meeting was also to devise ways to have the menstrual cycle accepted

and valued as a vital sign by providers who care for adolescent girls and young women.¹⁻² Clinical and basic scientists gave presentations that reviewed key topics in this area, with a plan to identify gaps in knowledge that would assist in formulating a research agenda. Throughout the meeting, attendees remarked that the approach to be used to carry out the research effort and the topics to be investigated are equally important. This chapter reviews the final discussion held on the concluding day of that meeting, and it is hoped it will serve as a manifesto to highlight the critical needs for additional research related to the menstrual cycle and adolescent health.

Keynote Address: Reflections on Fuller Albright and Patient-Oriented Research

Dr. D. Lynn Loriaux

The concluding chapter of the monograph from this meeting should represent a “dream.” The hope is to capture what the research agenda will look like for the next 100 years in the area of adolescent reproductive health, and specifically, the menstrual cycle and its applications to adolescent health and disease. There are many factors that require consideration as we ponder the next century and the research that should occur in this area. There are many lessons that can be learned about clinical research and how we approach this scientific effort if we consider the life of one of the most influential thinkers and medical scientists of all time, Dr. Fuller Albright.

First, we need to acknowledge that there is expanding knowledge in the area of genomics, and an enduring fascination with the link between genotype and phenotype. However, with these powerful tools in hand, we have to consider our “genetic citizenship.” In other words, the degree to which we are able to collaborate with one another in a fruitful collaboration and cross-exchange of ideas will dictate how well we are ultimately able to deliver answers to our patients. This type of collaboration relates to efforts aimed at understanding the underlying pathophysiology of a disease, or its optimal treatment. We have some information available for our use, but there still remain striking gaps in knowledge. For example, we have made significant gains in understanding the varying presentation of young women with premature ovarian failure (also known as “premature menopause”, or more accurately, “primary ovarian insufficiency”).³⁻⁴ However, we understand relatively little about how a genetic predisposition ultimately leads to alterations of ovarian function. An example is carriers of the fragile X mental retardation 1 (FMR1) premutation who have a 20-30-fold increased risk of developing primary ovarian insufficiency. The link between the predisposing gene (e.g., FMR1) and impaired ovarian function deserves further study. Ultimately, in any type of biomedical research aimed at improving health, the patient must be the “substrate” for investigation. The Greek word *pathos* means “sufferer.” Our future research has to be driven by meeting the needs of the sufferers in our society, and a healthy respect for the pathos associated with disease. .

Dr. James Wyngaarten, director of NIH from 1982-1989, wrote an article in 1981 entitled “The Clinical Investigator as an Endangered Species.”⁵ In 1974, close to the conclusion of the Vietnam War, there was a dramatic decrease noted in the number of individuals who held MD or MD/PhD degrees who applied for NIH funding to carry out biomedical research. These statistics were explained by fewer individuals choosing to pursue careers in biomedical research as the War was ending. In 1992, several years later, Edward H. Aherns, Jr., Emeritus Professor at Rockefeller University, wrote a book entitled, *The Crisis in Clinical Research*.⁶ He described the profound shift in emphasis from patient-oriented research to research at the cellular and molecular level. Ahrens argued that changes needed to be made in the training of clinical investigators and in their funding requirements, and

that new working partnerships between clinically skilled M.D.s and technically trained Ph.D.s were urgently needed to restore patient-oriented research to full productivity. He felt that a rebalancing should occur to assure that quality research resulted. To this day, there continue to be concerns that clinicians and scientists are becoming mutually exclusive, and for clinicians, scholarship can become a substitute for science. Both scholarship and science are important, but they have a different focus and mission.

Dr. Fuller Albright in his book, *Uncharted Seas*, had important insights into what features best characterize an outstanding clinical investigator.⁷ He wrote about this type of investigator as “a physician with a scientific habit of mind.” Albright concluded that this individual was equally comfortable in both the laboratory and on the patient ward. Another classic quote from that book is that “Many people see well, but neglect to look”(Albright).⁷ This description would *not* describe the astute clinical investigator who is constantly on-guard for any information that might provide a clue to help a suffering patient. Dr. Albright exhibited unprecedented devotion to his students and colleagues, and a relentless pursuit of knowledge. Even when severely afflicted by Parkinson’s disease, he continued to round with his students, residents, and Endocrine Fellows, who took copious notes for him while he continued to make important clinical observations, but he was no longer to hold his hand steady to write.

Translational research involves multidisciplinary efforts to bring about the most substantial biomedical advances over the next 100 years. There should be constant communication and dissemination of knowledge between the basic scientist at the laboratory bench, and the clinician or clinical investigator at the patient’s bedside. Work at the bench must be informed constantly by what is taking place at the bedside. It has been questioned whether the current system of grant evaluation renders the most benefit to physician-scientists or their patients. Perhaps the NIH or foundations should fund a person rather than a project? An example would be the Howard Hughes Foundation Program which grants stipends to individual scientists, each an outstanding principal investigator with a track record of success, to carry out work in a given area over a several year period. This funding then frees the scientist to put creative effort towards his or her research rather than spending countless hours preparing multiple grant applications to fund the efforts of the laboratory. This approach will require a process that will be able to identify and support the future “Fuller Albrights” relatively early in their careers.

Disease Research: Knowledge, Value and Innovation

Dr. Lawrence M. Nelson

Managing Innovation

In the effort to understand the underlying pathophysiology of or to discover a cure for a specific disease, specialists from diverse fields would ideally be brought together so that their talents, expertise, and ideas can be mixed. A “creative abrasion” would then result, which yields divergent, deep reservoirs of knowledge, but equally allows for diverse cognitive and communication styles to be juxtaposed.⁸ As Leonard said, “Innovation occurs at the boundary between mind sets.” Biomedical research is highly competitive. Tension can arise as issues related to intellectual property and authorship, and if not managed skillfully, may handicap collaborative efforts. Positive outcomes that can result from the intersection of differing styles include a consortium or alliance. Negative outcomes include predatory competition and efforts that violate anti-trust issues.

A research consortium can provide the proper structure for disease research. The proper structure shifts efforts towards knowledge creation, and away from resource and information hoarding. An example would be a genetic disease research consortium. Patients with a given

disease provide the focus, and a partnering with patients becomes the model. The National Fragile X Foundation illustrates these features, with disease researchers and their patients learning from each other, making it easy to work together, and sharing the efforts of their winnings. The Internet is also changing the way that patients and investigators interact with one another, inducing self-organizing behavior, aiding in information flow, and moving power to patient advocacy groups which may aid a consortium. However, this technology can also propagate misinformation. People and systems will self-organize when three vital ingredients are present: a higher common purpose, a willingness to work together, and a level of personal mastery and maturity.⁹ As Stewart said, "Intellectual capital is the sum of everything everybody in a company knows that gives it a competitive edge."¹⁰ It becomes clear that partnering increases intellectual power.

The organization of disease research consortia is multi-leveled. Patients and their families provide the focus. They provide the common shared goal that drives the effort. They also provide the reason for unity. Disease groups will eventually coalesce into a common research system. Consortia will collect, store, and distribute accurate clinical data on patients with specific diseases, and enable the collection of high-quality data, such as DNA and serum samples. The core sources will be patient-led groups, and DNA and data storage facilities. Other consortia members include: physician researchers, molecular geneticists, basic scientists, and individuals from pharmaceutical and biotechnical industries, academic institutions, and the NIH.

Knowledge

Creating a genetic map and finding genes creates information, but not knowledge. Data are a set of discrete, objective facts (e.g., a sequence of DNA). Information is data organized to convey a message (e.g., a gene). Knowledge is information in context, a fluid mix of framed experience, values, expert insight, and intuition (e.g., information utilized to understand and treat a disease). Knowledge exists at multiple levels, including the individual, group, organizational, and inter-organizational. In the collaborative research effort to approach a disease, examples of individuals who may work together include patients, physicians, and basic scientists. Groups include patient support groups and research consortia. Organizational efforts include repository facilities, the pharmaceutical and biotechnical industries, academic institutions, and the NIH. Ideally, inter-organizational research endeavors would occur in which individuals of varying and complementary backgrounds collaborate for the common good. The most innovative projects will bring individuals together from different fields. Knowledge permits action, and in biomedical research, this means knowing how to prevent, detect, or treat disease.

Value

In disease research, efforts should focus on the needs of patients in order to create the greatest value. The research then stems from what the patients need. A research team must develop and nurture the competencies needed for innovation. Ultimately, the research team must translate the knowledge created by these competencies into action for patients. The goal is to create knowledge that is of value to patients.

Insights from Two Outside Experts

Dr. Melvin Grumbach

To carry out disease research effectively, one must organize task forces (study groups) using a multidisciplinary approach, including pediatric endocrinologists, adolescent health experts, reproductive endocrinologists, behaviorists, neuroscientists (including neuroendocrinologists), experts on evolutionary and life history theory, experts on prenatal,

perinatal and infancy events that influence disease and disability in later (adult) life, systems biologists, experts in development of patient databases and “biobanks”, and experts in “omics” (genomics, proteomics, metabonomics, pharmacogenomics), population geneticists (including experts in quantitative trait loci, and biomarkers), and economists. Knowledge has expanded so dramatically over recent years that it will take a well-organized team of diverse individuals to solve the most complex of medical problems.

Genetic research continues to advance and diagnostic possibilities exist that were never possible before. However, we must ask ourselves the question, “How can we best prepare ourselves for the “thousand dollar genome”—the time when genomic sequencing becomes commonplace, the era of “personalized medicine” and “personal genomics”? Within this new framework, what can we learn about puberty and the menstrual cycle?

The existence of the “Electronic Medical Record” (EMR), which will have an enormous amount of up-to-the-minute databases, will have important implications for patient-oriented research. The EMR promises to revolutionize data collection and management for clinical research and epidemiologic studies including issues related to puberty and the menstrual cycle. It also provides a method of accumulating ongoing follow-up data.

Research Areas of Priority over the Next 100 Years

- Take into account consideration of “human life history,” including Gluckman and Hanson’s predictive adaptive response (PAR), 11 and the evolution of human maturation. More specifically, research in this area would include an in-depth, inclusive examination of factors influencing the age of menarche (including prenatal and postnatal influences on timing of menarche).¹²
- An important long-term goal would be to understand the molecular mechanisms that drive the cellular processes that result in “puberty”.
- An improved understanding of the interaction between the brain and both the reproductive endocrine system and growth hormone cascade. There are still gaps in knowledge regarding the organizational effects of brain peptides on sex hormones and their receptors (e.g., oxytocin and its effect on expression of estrogen receptors in the brain).
- An improved understanding of the relation between stress hormones, behavior, and puberty.
- An understanding of how receptors in brain cells and their ligands are associated with pubertal maturation (e.g., GPR54 [a G-protein coupled receptor] and its ligand, kisspeptin and genes expressing and regulating this system). Equally important is an understanding of the role of neuroexcitatory amino acids (e.g., glutamate), neuroinhibitory neurotransmitters (e.g., GABA), and growth factors on pubertal maturation. For example, inactivating mutations of GPR54 result in autosomal recessive hypogonadotropic hypogonadism (Seminara).¹³ In contrast, a polymorphism in GPR54 gene appears to be correlated with precocious puberty in some cases, likely as a result of changes in expression of the receptor.¹⁴
- An understanding of the relationship between hormones, bone maturation, and epiphyseal fusion. There remain unknowns as related to mechanisms (systems biology). The exact role of vitamin D, calcium intake, parathyroid hormone, calcitonin, among other variables (exercise, skeletal loading) is still unclear with respect to both bone accretion and growth plate biology.
- Research should be carried out to examine the relationship between puberty and bone health. We need to improve methods for measuring bone deposition and bone

resorption, and measuring bone mineral density (including both cortical and trabecular bone) in the growing child and adolescent. We are currently limited by shortcomings in our measurement tools to evaluate various aspects of bone density and skeletal health. It is important to identify if there is an increased fracture risk *in adolescents* with delayed adolescence, hypogonadism, anorexia nervosa. Longitudinal studies that document whether the risk of osteoporosis and fracture is increased in these patients would also be informative and could help in the formulation of health guidelines and policy.

- Polycystic ovary syndrome (PCOS) is a common syndrome among adolescent girls and is deserving of continued attention and research. The relation of prenatal events to development of this disorder is unclear. The role of obesity and abdominal adiposity, insulin resistance, and dyslipidemia in affected adolescents and young women should also be examined.
- An important area to explore is the improvement of serum assays and other measurement tools, a gap in knowledge that currently handicaps both the clinician and clinical investigator. Needs include providing better standardized, more precise, sensitive, and highly specific method for measuring low concentration levels of estradiol (and testosterone) in plasma of children and adolescents. Many of the present commercial kits and assay platforms are exceedingly inaccurate and expensive.
- There are now powerful tools available to investigate the molecular biology and genetics of spermatogenesis, ova maturation, which will have important implications for health care.
- The relationship between circulating sex hormones and risk-taking behaviors in adolescents deserves further study.

Dr. Alan Rogol

Many of the same areas were identified by both Drs. Rogol and Grumbach as research topics of priority. Many of Dr. Rogol's reflections relate to areas that can be classified as representing the biosocial sphere of adolescents. An important recent position statement on the 'Female Athlete Triad' was published by the American College of Sports Medicine that reviews the energy and stress aspects of pubertal maturation, bone, and the menstrual cycle. 15 The Triad encompasses disordered eating, amenorrhea, and osteoporosis in a young female athlete. This publication is an important one for the field of adolescent reproductive health. A better understanding of how energy deficits mediate hormonal abnormalities, ultimately responsible for skeletal deficits and other problems, will represent a significant advance in the field.

A multidisciplinary team will be needed to address the complex research agenda of the next 100 years. In addition to members of the team identified by Dr. Grumbach, other invaluable team members would include auxologists and population biologists. The perspective of auxologists on work biology and fertility for a *population* has relevance to the study of the menstrual cycle. Psychosocial stress, in addition to energy availability, has direct relevance to maturation and an understanding of the etiology of secondary amenorrhea.

Research areas of Priority

- Great emphasis should be placed on the importance of the effects of human life history on both development and potential alterations of the menstrual cycle. Gluckman and Hanson's predictive adaptive response (PAR) is important to consider in delineating how stress may alter active biological processes (e.g., the

menstrual cycle) in a young woman.¹¹ An understanding the link between stress hormones and both behavior and pubertal development would be an important part of this general goal.

- The prenatal condition has a strong relationship to puberty including early (and rapid) pubertal development. Understanding the mechanism would not only help these individuals, but will bring in the problems of insulin resistance and hyperandrogenemia. An example of collaborative efforts that lead to multidisciplinary collaborative work and understanding of a problem is the recent consensus conference and statement organized by international societies of pediatric endocrinology and the Growth Hormone Research Society.¹⁶
- There is increasing information becoming available regarding the relation between receptors in brain cells and the timing of puberty. An understanding of known factors is needed, as well as a search for other factors (up- or downstream).
- Bone health is an extremely important concept to consider in the adolescent, and in particular, the relationship of bone density and fracture risk to puberty and the menstrual cycle. Osteoporosis is not a disease of middle-aged women; in reality, it is a preventable disease of pre-pubertal children. There are data that show an increased risk of fractures that occur around the timing of the growth spurt in girls and boys.¹⁷ There is a surprising lack of uniform recommendations in this area as related to nutrition and exercise with respect to bone health. There is still work to do to understand the relation between calcium and vitamin D intake (both dose and duration), and activity and the eventual development of peak bone mass. Research in this area would yield information that makes possible the formulation of pediatric nutrition and exercise guidelines, with the final goal of optimal bone health.
- PCOS is a common problem that represents a multi-faceted disorder with many long-term health sequelae. An emphasis should be placed on finding the root causes of insulin resistance, given that it is likely the mechanism likely responsible for the disordered puberty and abnormalities in menstrual cyclicity seen in some SGA children, and especially in those who are obese. Five to 7 percent of women have PCOS¹⁸ and many more exhibit insulin resistance,¹⁹⁻²⁰ and these teenagers and young women are at high risk for the development of type 2 diabetes mellitus. ¹⁸⁻²⁰ Therefore, an emphasis should be placed on understanding the link between insulin resistance and the function of the hypothalamic-pituitary-gonadal (HPG) axis, as this problem affects not only adolescents, but is a major public health problem of reproductive-age women.
- An important priority for any investigators in the area of reproductive health is to develop accurate and sensitive assays to measure sex hormones. There are a number of groups working on biological assays that measure all androgen receptor-stimulating (and inhibiting) compounds and similarly for the estrogen receptor. In addition, better gas chromatography/mass spectrometry (GC/MS) assays are being developed for a specific androgen (e.g., testosterone) and estrogen (e.g., estradiol). Depending on the interest of a clinical investigator, one could focus on either set of assays.
- The future research agenda should integrate physical exercise more than has been previously noted. The population biologists often focus on the work product of malnutrition that may be stunting the growth of workers, makes them poorer “machines” to produce work as adults. Similar points, including (energy availability) and physical work, are important to consider in understanding pubertal development and the menstrual cycle (how many babies do they have) and the

“quality” of the work (with reference to bone mineral accrual and attainment of the highest possible peak bone mass).

- There are data about the timing of menarche with relationship to birth order and mother’s age of menarche.²¹ Stress aspects, as noted previously, likely have some relevance to understanding these processes.
- The genome will be a powerful research tool, especially if one can obtain it relatively inexpensively. However, many of the single gene difficulties are already known or will be relatively easily found. It will be important to consider gene-gene interactions and their impact on a biological outcome (e.g., height). Bioinformatics and computing power will be key issues. This is not to suggest that the 100 year view of the reproductive cycle needs specific bioinformatics, just that there should be individuals evaluating the newer aspects of bioinformatics to see what may be useful in the biological studies that have been suggested.
- Research on endocrine disruptors will be important over the next 100 years as these are real (not theoretical) problems in the animal and human world.²²⁻²³ They will likely affect the number of species that thrive and the population biology of both men and women [and the pathway (adolescent development) by which they get there]. This issue will be one to consider in the development of new assays, as well as interactions with the genome. It is suspected that those with “different” detoxifying pathways would react to environmental disruptors along a spectrum, which makes their identification and understanding of biological effects more complex.

Summary of Discussion Groups

Four breakout groups were assembled from among the meeting attendees. The specific goal assigned to each group was to develop an agenda that would set the stage for how research should be conducted over the next 100 years, and to identify the pressing research questions that should be addressed as they relate to the menstrual cycle and adolescent health. The four areas represented in discussion groups included: 1) emotional health research; 2) metabolic and reproductive research; 3); genetic research; and 4) promoting the conduct of clinical research.

Emotional Health

A number of important objectives were generated by the emotional health research group. The ultimate goal of research in this area should be for girls and young women to have a strong sense of well-being. The first objective identified was to understand the perceptions of the menstrual cycle by girls and their families within a cultural context. Specifically, how do these perceptions impact on their sexual behaviors, contraceptive choices, nutritional choices, and physical activity? A biomedical outcome that would be affected by nutrition and activity choices is weight. A second objective was to understand how girls with menstrual abnormalities and their families make healthcare decisions. This objective would include exploring how they seek health care, adhere to treatment, and manage the emotional adjustment of being diagnosed with a health problem. The last objective identified by the group was to determine the psychosocial needs of girls with chronic medical conditions and their families with regard to: making menstrual management decisions, sexuality, and future reproductive potential.

This group also discussed a number of other topics. They suggested that the concepts of emotional health be included in large, representative studies of adolescents (e.g., National Health and Nutrition Examination Survey (NHANES), Add Health, etc.) Questions could

also be added to existing questionnaires for ongoing studies that currently lack domains related to emotional and reproductive health. The Centers for Disease Control and Prevention should be encouraged to consider increasing preventive efforts in the area of reproductive health and the menstrual cycle. Many current research studies focus on biomedical outcomes. Qualitative research in the area of emotional health related to the menstrual cycle would likely more accurately capture both the current understanding and impact of past experiences of adolescent girls and their families. Lastly, complementary to what was discussed by one of the other subgroups, longitudinal studies need to be designed that specifically examine the relationship between biological outcomes and psychosocial influences surrounding puberty and the menstrual cycle.

The most significant obstacle identified by the group which hinders research in this area is that investigators are not asking the appropriate questions. Unfortunately, current questions that are posed often contain unknown biases. Thus, many questions posed to adolescents are flawed, and investigators are unaware of the problem; therefore, errors continue to be propagated. Specifically, many investigators do not consider cultural differences that may be present as a question is asked. Two solutions were discussed to remedy this problem. First, standardized questionnaires could be developed that could be used by both national and international representative (or population) studies, as well as by disease-specific networks. Second, a standardized set of core questions could be developed for both hypothesis-generating and hypothesis-confirming studies.

Metabolic and Reproductive Research

This group proposed the need for a Study of Puberty across the Nation (SPAN). This would be similar to the Study of Women's Health Across the Nation (SWAN) Study, a multiethnic study about menopause. This prospective multi-center and multi-ethnic study would enroll children, adolescents and young adults, age 9-24 years, in order to provide prospective data on several health outcomes. A priority set by this group was the important relationship that exists between puberty and bone mineral accretion. A goal of the study would be to obtain information related to several health outcomes or biological processes (e.g., pubertal maturation), each a variable known to affect bone density, a primary outcome of the study. It was also acknowledged that osteoporosis is considered by many experts to be a "pediatric disease," in onset and important to prevention with risk factors for hip fracture among other skeletal outcomes suspected to emanate from factors during the childhood and adolescent years.²⁴ Information would be obtained in a variety of areas, providing for a rich, multi-faceted database. The types of data collected would include: anthropometric, dual-energy x-ray absorptiometry (DXA, bone density and body composition), peripheral quantitative computed tomography (pQCT) (bone density, geometry, and strength), bone turnover markers, menarche and the menstrual cycle, banked DNA, selected disease markers, and Tanner pubertal staging. It was acknowledged that there is currently a paucity of data relevant to what constitutes the normal range in for several of these variables. Therefore, a primary contribution of the study would be the collection of reference data for bone density, bone turnover markers, and body composition in normally growing and developing children and adolescents, among other endpoints.

The group stated that a large final sample size would be needed to provide the most accurate normative data and to draw accurate conclusions. Therefore, the multi-center approach would enable clinical investigators at each site to collect data in a uniform way to permit the findings to be pooled. A limitation of individual investigator-initiated projects is that the small sample size from one site can limit the generalizability of the findings. In addition, if different assays, DXA scanners or methods for assessing pubertal status are used, the results from multiple centers cannot be combined. The SPAN Study, in which outcomes and uniform measurement tools would be identified *a priori* and collaborations developed before

data are collected, would circumvent many of the current problems which have hindered the establishment of reference data. An obstacle identified by the group to the collection of these important data is funding. Therefore, it was hoped that an application to the NIH could be submitted that includes multiple principal investigators (PI) to carry out the research effort. Allowing a single application to have multiple PIs was noted as a more feasible way to enable an academic clinical investigator, who has to balance the competing demands of clinical research, patient care, and teaching, to carry out this work in a timely way.

Genetic Research

This group stated that genetic questions of priority in the area of adolescent reproductive health should be mindful of those with the broadest appeal and clinical application. It was acknowledged that there is still much to understand regarding the biology underlying oogenesis, the first step in the complex process of reproduction. Premature ovarian insufficiency (POI) was identified as a problem for which a surprising amount is still unknown. It was recommended that a whole genome association approach be used in an effort to understand the causes and predisposition to POI, including the enrollment of ethnic-specific controls to identify POI genes. The whole genome approach can be especially helpful if a clear marker has been identified, as is the case in young women with POI. Specific diseases known to cause alterations in ovarian function (e.g., Turner syndrome, galactosemia, *FMR1* premutation, etc.) may be used as models to determine the relative contribution of prenatal and postnatal variables to the ultimate clinical phenotype. One particularly appealing model would be longitudinal population-based studies of women who possess a premutation in the *FMR1* gene, a single gene cause of altered ovarian function. A prospective research model could be organized that would assess the incidence of altered ovarian function in this population, future effects of disease, and the pathologic mechanisms underlying the associated abnormal ovarian function. The primary approach here will be bedside to bench, and then bench back to bedside.

Promoting Conduct of Clinical Research

Throughout the meeting, the concern was raised by numerous individuals from varying disciplines that the current regulations are handicapping the creative effort of investigators. Therefore, one discussion group was assigned to discuss ways to facilitate translational research in adolescent health (from bedside-to-bench and back), including gonadal function and its impact on reproductive, bone, and psychological health and well-being.

Problems recognized included a prolonged and inefficient review process that is required for each individual research protocol including: General Clinical Research Center (GCRC), Institutional Review Board (IRB), institutional/legal-NIH-regulatory (Office for Human Research Protections (OHRP), Food and Drug Administration (FDA) applications and ultimate approval; a lack of unification of scientific and IRB review which delays the process; lack of direct communication between investigators and their local IRB, which prolongs final approval because of miscommunications that are generated; guidelines for minimal risk are not clearly defined; and the existence of excess bureaucracy in the review of protocols and consent forms (HIPPA). Other problems cited include a lack of recognition that the adolescent level of risk is unique (e.g., pregnancy potential) and not age-related (i.e., stage-related). Lastly, debt accrual by potential clinical investigators often forces them to enter clinical practice over academic research because of financial concerns. The frustrations generated by excessive regulatory issues can discourage a young scientist who was considering a potential career in clinical investigation.

Solutions to recognized problems were also generated and discussed. Proposed recommendations included that the Secretary's Advisory Committee on Human Research

Protections (SACHRP) direct OHRP to give IRBs clear guidance on minimal risk, thereby streamlining the research review process in ongoing collaboration with the research community. More specific recommendations included that NIH develop a flexible, speedy process of funding translational research teams directly. Professional societies should also develop guidelines and consumer education materials to promote translational research. General suggestions identified by the group included that investigators be encouraged to interact directly with their local IRB. It was felt that this interaction would facilitate communication and avoid needless delays in the approval process. Attempts should be made to avoid the multiple obstacles that exist for investigators as they try to enroll healthy control subjects to carry out a well-designed clinical trial. Lastly, it was recognized that promoting adolescent menstrual cycle research is “preventive medicine” for adult disorders, therefore making it a priority area as research agendas are being generated.

Incentives for Expanding Numbers of Clinical Investigators

There is a need to expand the research work force in the area of the menstrual cycle and adolescent reproductive health. A suggestion for increasing numbers of clinician-researchers is to have the cost of malpractice insurance covered by a governmental program set up for this purpose. Attendees at the meeting cited the cost of insurance as a difficult obstacle for physicians to spend half or more of their time on what may be viewed as less lucrative research. There was also discussion around the NIH and other federal agencies considering the projected productivity of an outstanding individual scientist, rather than the current system of assessing the scientific merit of individual projects. Dr. Loriaux referred in his keynote address to a model in which the NIH “fund the person, not the project.” The current system hinders the creative effort and slows the advancement of current research as an extraordinary amount of time is spent by a PI in the preparation of grant applications to keep a laboratory or research group funded. The NIH Loan Repayment Program (LRP) has been met with tremendous success as young physician-scientists are able to pursue patient-oriented research in exchange for loan forgiveness. This type of program will enable young scientists to make decisions driven by their interests and personal commitments to a cause, rather than having to be burdened by the financial constraints generated by college and medical school expenses.

Summary

Research in adolescent reproductive health, and specifically, related to the menstrual cycle should be a high priority for the NIH and other funding agencies. Many disease processes emanate from problems during the adolescent years. Absence of or the presence of irregular menses can be a clue to their presence, which if identified early and treated, and prevent more serious long-term health outcomes. Examples discussed include type 2 diabetes in an adolescent with PCOS and later osteoporosis in a teenage adolescent athlete with amenorrhea. Both the specific topics that comprise the research agenda and the process of how the research is carried out are equally important considerations. Research consortia centered on a specific disease represent a feasible structure to carry out work both effectively and in a timely way. Involving the work of patients and their families, and that of both clinical and basic investigators, results in research with the broadest application. There remain concerns that the clinical investigator is an endangered species. Several thoughtful incentives have been suggested to nurture young investigators as they make long-term career decisions. This must become a priority for these young scientists will become the next generation to carry out investigation in the area of the menstrual cycle and adolescent health.

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