0031-3998/02/5101-0119
PEDIATRIC RESEARCH
Vol. 51, No. 1, 2002
Printed in U.S.A.

SPECIAL ARTICLE

American Pediatric Society Presidential Address 2000: Reflections on the 20th and 21st Centuries

REBECCA H. BUCKLEY

Duke University Medical Center, Durham, North Carolina 27710, U.S.A.

It has been an honor and very great privilege to serve as President of the American Pediatric Society at the end of the 20th Century and in this historical year when four major North American Pediatric organizations are meeting together for the first time at the beginning of another century. The unique timing of this Address has allowed me to reflect on some of the remarkable changes that occurred in Pediatrics during the 20th Century and on the many more changes envisioned for future.

MAJOR SCIENTIFIC ADVANCES OF THE 20TH CENTURY

When President Henry Koplik spoke 100 years ago before the May 1900 meeting of the American Pediatric Society, he discussed approaches for the control of summer diarrheal illnesses, suggesting that hospitals were likely to spread such diseases and advocated outpatient care. Other topics in that year were polio and lead poisoning. However, in the history of this Society, there was no mention of his reveling over scientific accomplishments of the preceding Century (1). I present to you here a series of tables, contributed by some of my pediatric colleagues, listing some of the most important advances in their subspecialty during the past century. These lists are not meant to be all-inclusive. Starting first with infectious diseases (Table 1), major advances far antedated the discovery of antibiotics, simply through improved public water supplies and sewage treatment. Unquestionably, the advent of antibiotics has had an enormous impact, but vaccines to prevent many of the most devastating illnesses have been even more important. The newest is the conjugated pneumococcal vaccine that was just released in April of this year.

Some of the major advances in neonatology during the last century are listed in Table 2. I don't need to tell any of you how much of an impact these discoveries have had on care of the newborn, no matter how small. Despite these major technological and scientific accomplishments, however, the United States still ranks 25th in infant mortality among developed nations. Thus, dissemination of information as to how to lower this mortality remains a challenge for the 21st Century. Advances in hematology and oncology have been no less impressive (Table 3). Rh disease has been essentially eliminated. Modern chemotherapy has allowed a greater than 70% cure of childhood malignancies, and both blood product support and bone marrow transplantation have enabled mitigation or cure of conditions for which there was previously no effective treatment.

Some of the chief accomplishments in pediatric pulmonology are listed in Table 4. These include, among others, the development of mechanically assisted ventilation for respiratory failure and the discovery of the gene that is mutated in cystic fibrosis. Development of an effective treatment for the nephrotic syndrome and kidney transplantation for patients with end-stage renal disease are some of the remarkable accomplishments in pediatric nephrology (Table 5). Advances in

Table 1. *Some advances in the control of infectious diseases during the past century**

- Improved public water supplies and sewage treatment (which in turn decreased infant mortality and reduced infantile diarrheas). Indoor plumbing also decreased some parasitic diseases
- Antibiotics—all of them. Sulfas were first
- Vaccines
  - Smallpox
  - Measles
  - Polio
  - Hemophilus influenzae
  - Varicella
  - Pneumococci
- Treatment and control of tuberculosis
- Discovery of HIV disease in children

* Contributed by Dr. Ross E. McKinney, Jr. of Duke University.

Table 2. *Some advances in neonatology during the past century**

First 50 years
Incubators for temperature control
Development of infant formulas
Oxygen therapy
Cardiorespiratory monitoring
X-rays
Application of the scientific method
Last 50 years
Improvements in intravascular access
Continuous positive airway pressure
Continuous flow mechanical ventilation
Formulas for premature infants
Discovery and therapeutic application of surfactant
Noninvasive imaging

* Contributed by Dr. David Tanaka of Duke University.

Correspondence and reprint requests: Rebecca H. Buckley, M.D., Box 2898, Duke University Medical Center, Durham, North Carolina 27710, U.S.A.; e-mail: BUCKL033@mc.duke.edu

Table 3. *Some advances in hematology/oncology during the past century**

- Elimination of Rh disease
- Modern chemotherapy for childhood malignancies (>70% cure rate today)
- Hematopoietic growth factors
- Blood product support
- Clotting factor replacement (especially cloned factors)
- Bone marrow transplantation for inborn errors of hematopoiesis and malignancies

* Contributed by Dr. Philip Rosoff of Duke University.

Table 4. *Some advances in pediatric pulmonology during the past century**

- Development of mechanically assisted ventilation for respiratory failure
- Development of complete pulmonary function testing, standards, and equipment for all ages
- Development of diagnostic and therapeutic applications of fiberoptic bronchoscopy
- Discovery of structure and function of CFTR and its gene(s) for cystic fibrosis
- Pediatric lung and heart-lung transplantation

* Contributed by Dr. Thomas Murphy of Duke University.

Table 5. *Some advances in pediatric nephrology during the past century**

- Steroids for idiopathic nephrotic syndrome: 50% 5 years mortality in 1930, currently <5% mortality over 20 years
- End-stage renal disease management: improvements in kidney transplantation have changed survival from <30% at 5 years to 75% now
- Growth hormone, calcitriol, and erythropoietin now prevent or correct rickets, short stature, and anemia of chronic renal disease

* Contributed by Dr. John Foreman.

gastroenterology have been no less impressive (Table 6), with the development of oral rehydration solutions for severe diarrhea, the technology and science of total parenteral nutrition, and liver transplantation for end-stage liver disease among the many achievements.

Seminal discoveries in endocrinology are listed in Table 7, starting in the early part of the century with discoveries of thyroid, pancreatic, adrenal, and hypothalamic hormones and ending with the more recently elucidated molecular structures of hormone receptors and the purification of GH. Probably no field has advanced more over the past 100 years than genetics (Table 8)—all the way from the first description of Mendelian inheritance in humans and the first inborn error of metabolism in 1902 to the nearly complete sequencing of the human genome in this current year.

In my own subspecialty, there have been many remarkable advances as well. In immunology (Table 9), these range from the discovery of antibodies in the gamma globulin fraction of serum in the first half-century to the discovery in the last half-century of the roles of the thymus gland and other lymphoid organs, the identification of the phenotypes and functions of various lymphocyte subpopulations, and the molecular characterization of surface molecules and secreted factors from lymphocytes and other cells that are necessary for adequate immune responses.

Table 6. *Some advances in gastroenterology during the past century**

- Development of effective oral rehydration solutions for cholera and other infectious diarrheas
- Development of technology and science of total parenteral nutrition
- Development of pediatric endoscopy (diagnostic and therapeutic)
- Discovery that *Helicobacter pylori* infection causes gastric ulcers
- Pediatric liver transplantation (cadaver, living-related)

* Contributed by Dr. William Treem of Duke University.

Table 7. *Some advances in pediatric endocrinology during the past century**

- Isolation of thyroxine by Kendall in 1915
- Discovery of insulin by Banting and Best in 1921
- Identification, isolation, and purification of adrenal steroids 1927–1954
- Isolation of hypothalamic hormones by Schally and Guillemin in 1969
- Elucidation of hormone receptors by Jesse Roth, Ira Pastan, and Robert Lefkowitz
- Purification of growth hormone by C. H. Li

* Contributed by Dr. Michael Freemark of Duke University.

Table 8. *Some advances in genetics during the past century**

- 1902, Garrod, first description of Mendelian inheritance and inborn error of metabolism in man, alcaptonuria
- 1949, Pauling and Ingram, sickle cell disease results from change in a single amino acid in a protein
- 1956, Tjio and Levan, 46 human chromosomes
- 1986–89, first positional cloning of disease-causing genes, chronic granulomatous disease, and cystic fibrosis genes
- 2000, near completion of human genome sequencing

* Contributed by Dr. Y. T. Chen of Duke University.

Table 9. *Some advances in immunology during the past century*

- Identification of antibodies in the gamma globulin fraction of serum
- Discovery of the roles of the thymus and other lymphoid organs
- Identification of phenotypes and functions of lymphocyte subpopulations
- Molecular characterization of surface molecules and secreted factors from lymphocytes and other cells necessary for adequate immune responses

In allergy (Table 10), the discovery of IgE by Kimi Ishizaka in 1967 (2), the elucidation of the roles of the many mast cell mediators in allergic inflammation, the identification of T cell and mast cell cytokines that promote allergic responses, and the development of promising new treatment strategies based on this knowledge.

Probably no information base has grown more rapidly than that of the primary immunodeficiency diseases (Table 11) (3). Nothing was known of these conditions until the last half century, beginning with the report of Swiss type agammaglobulinemia in 1950 (4) and Ogden Bruton's discovery of agammaglobulinemia in 1952 (5). Since then, more than 95 different immunodeficiency syndromes have been described and, remarkably, the molecular bases have been identified for more than 2 dozen of them just within the past 7 years (3).

Advances in the ability to treat these diseases have also been astounding. In addition to the ability to provide missing antibod-

Table 10. *Some advances in allergy during the past century*

- Discovery of IgE by Dr. Kimishigi Ishizaka
- Demonstration of roles of the mast cell and basophil in allergic inflammation
- Identification of a subpopulation of T cells that promotes allergic responses by secreting IL-4, IL-5, and IL-13
- Development of treatment strategies that target IgE, IL-4, or IL-5

Table 11. *Some advances in the understanding of human immunodeficiency during the past century*

- 1950–1952: first discovery of humans with missing antibodies, cell-mediated immunity, or both
- 1999–2000: more than 95 different primary immunodeficiency syndromes now recognized
- 1993–2000: molecular bases of more than 2 dozen defects identified in short period of time facilitated by the Human Genome Project

ies, first intramuscularly and now intravenously, cellular therapy has also proved to be life-saving for an ever-growing number of infants and children afflicted with these disorders (Table 12). The first successful immune reconstitutions by unfractionated HLA-identical bone marrow transplants were reported in 1968, just after the discovery of HLA (6). However, until 1981, such transplants were successful only when there was an HLA-identical sibling. Since then, rigorous T cell-depletion techniques have permitted the use of half-matched parents as donors, opening this treatment possibility to virtually all affected with SCID (7). Most remarkable of all, Alain Fischer's group in Paris just reported in Science the first truly successful human gene therapy in two infants with X-linked SCID (8).

These lists have been only examples of the many scientific accomplishments of the past century. There are obviously many more, and I didn't even list examples in Cardiology, Neurology, or Critical Care Pediatrics. The point is that these discoveries have improved countless lives and they provide the groundwork for many more discoveries yet to come. It should be noted that, while some discoveries occurred by serendipity, most were made through application of the scientific method. Even the serendipitous ones required the appreciation by a prepared mind of the significance of the finding.

CHALLENGES FOR THE 21ST CENTURY

So what can we expect in the next century? For discovery to continue we must preserve academic excellence. I have heard it said many times in recent years that pediatric faculty can no longer be expected to be "triple threats." Because of this, there has been a tendency to segregate faculty into "clinical" and "research," and many institutions now have distinct tenure tracks for each type of faculty. Faculty are then hired whose responsibilities are to see patients and do clinical teaching and possibly some clinical research, but they are not expected to apply for research grants. Obviously, the financial support for such faculty must come from clinical dollars. The creation of tenure tracks for these clinician/teachers has created guidelines whereby they can be promoted. However, since the expectation is that such faculty will generate sufficient clinical dollars to cover their (and possibly their secretaries') salaries, the push to do so leaves them little time for scholarly pursuits. The research faculty on the other hand will not be expected to see many, if any, patients but will be expected to generate most if not all of their salary from grants. Thus, they spend most of their time writing grants and doing research. In the process, that person soon finds him or herself losing clinical skills.

Table 12. *Some advances in cellular and gene therapy during the past century*

- 1968: successful corrections of SCID and Wiskott-Aldrich syndrome patients' defects with unfractionated HLA-identical allogeneic bone marrow stem cells
- 1982–2000: successful application of rigorous T cell-depletion techniques permits use of half-matched mother or father as marrow donors for immune reconstitution of SCID infants
- 2000: first truly successful human gene therapy accomplished in France in two infants with X-linked SCID

This problem was not overlooked by those who wrote the FOPE II report (9). This is a direct quotation from that report, *i.e.* the statement is made that "the pediatrician-scientist of the future will not only need to be educated to provide the highest standard of care for children but also must acquire the skills necessary to conduct independent, funded research, to educate other health care providers, and to serve as the principal consultant to all health care providers involved in caring for children with severe, complex or rare disease."

The solution, in my view, is to resurrect the physician-scientist. There is obviously going to be an enormous need for physician-scientists in the next century. With the entire human genome now having been almost completely sequenced, the challenge is just beginning. For many (if not most) genes, the biologic functions will need to be elucidated. This will be done to some extent by animal models in which the gene in question is deliberately mutated. However, there are already many examples of how the phenotype of "knockout" mice is very different from that of humans who have the same gene mutated. Thus, a continuing search for human disease-causing genes will be needed. This will have to be done by physician-scientists who care for patients for whom the molecular bases of their diseases remain unknown. The molecular techniques have and will continue to be improved such that many of these will be automated or done with kits. The previous emphasis on molecular biology training will have to be modified with the major emphasis on the biology part. Our patients pose the questions and they always stimulate us to find the answers. They are our best teachers!

In addition to being creators of new knowledge and having the ability to translate new discoveries from the bench to the bedside, physician scientists will be key to the practice of evidence-based medicine. Many, if not a majority, of the parents of our future patients will have already gone on-line to the World Wide Web and have read in depth about their children's problems before seeing a physician. All pediatricians must have time for continuing medical education, but physician-scientists will have the greatest knowledge base and should have more time to allow that to grow. By fulfilling all of these roles, they will serve as the mentors and role models for the physician scientists of the future.

Physician scientists need to maintain their clinical skills through at least a half-day clinic and limited attending rounds to be able to provide state-of-the-art clinical care and to be good mentors and role models. The rest of their time should be protected for their research, and they should also not be burdened by administrative chores or the need to generate clinical dollars to provide their salaries. However, they would and should be expected to teach medical students, residents, and postdoctoral fellows.

Academic health institutions are clearly in a desperate state, and some are having to close. Currently there are two main sources of income–dollars generated from clinical care, and faculty salary support on research grants. Much smaller amounts come from state funds (for state institutions), endowments and tuition. Medical education is the component that has never had sufficient funding, and the government contribution to that has always been linked to patient care revenues. In the FOPE II report, it is proposed that a multipayer system be created to fund the entire spectrum of medical education (9). It is envisioned that educational dollars would flow into a national medical trust fund administered by a nonpartisan mechanism. This is a bold new proposal and one that is vital to the future of academic medicine. These institutions also need to have funds budgeted for the portions of salaries of their faculty that are not covered by grants.

As noted in several previous presidential addresses, the economic crisis in medicine led in the mid-1990s to a "brain-drain" away from specialization and toward general pediatrics. Many of the brightest residents were lured to managed care organizations by attractive salaries as a way to pay off their medical school debts. This resulted in a several year hiatus with little replenishing of our subspecialty man- and woman-power. How can we replenish the academic enterprise? The obstacles are the enormous debts that medical school graduates have incurred, which had risen from a mean of approximately $33,000 in 1986 to nearly $87,000 in 1998. There has also been pervasive pessimism over opportunities for research funding and for academic advancement. In the FOPE II recommendations, it is proposed that there be federally sponsored debt forgiveness for those who choose to do fellowships with careers in academic medicine (9). This would relieve the huge financial pressures on those aspiring for academic careers and also counter the frequent argument against entering a subspecialty, *i.e.* that subspecialists don't make much more money than general pediatricians–except for those subspecialties that are procedure oriented. Finally, we have to shore up the research infrastructures of those academic institutions that are not currently in the top ten in research dollars awarded.

Moy and associates of the AAMC reported a disturbing finding in the *New England Journal of Medicine* in January of this year (10). In this report, it was found that the 10 most research-intensive medical schools, as defined by having the most National Institutes of Health grants in 1986, still had the most National Institutes of Health grants in 1997 (Table 13). In fact, the percentage of all National Institutes of Health awards to these top 10 schools had increased from 24.6% in 1986 to 27.1% in 1997. By contrast, the 75 least research-intensive schools received proportionately fewer awards (declining from 24.3% in 1986 to 21.8% in 1997). This is not necessarily surprising, since success breeds success. However, it means that residents and fellows in the least research-intensive institutions do not get exposed to much peer-reviewed, cutting-edge research; therefore, they have fewer academic career role models. If we are to equalize the distribution of grant awards, then the least research-intensive schools will need to focus on increasing their research faculty and research infrastructures, otherwise the rich will continue to get richer. On the positive side, the increased proportion of awards to top-10 schools consisted primarily of increases in awards to clinical departments. Basic-science departments received a smaller proportion of awards than clinical departments, both in 1986 and 1997. Thus, the notion that one has to be a truly basic investigator to obtain funding appears to have little basis in fact.

Table 13. *Distribution of NIH Research Awards**

- Between 1986 and 1997, the proportion of research awards granted by the NIH to the 10 most research-intensive medical schools increased from 24.6% of all awards to 27.1%.
- The proportion to the 75 least research-intensive medical schools decreased from 24.3% to 21.8% of all awards.
- The increase to the top 10 schools consisted primarily of increases in awards to clinical departments. Basic science departments received a smaller proportion.

* Moy et al., N Engl J Med 342:250–255, 2000.

I am happy to report that, in contrast to the recent drought, there are definite signs that the number of pediatricians entering fellowships is increasing. Shown in Table 14 are data provided by Dr. James Stockman of the American Board of Pediatrics regarding the numbers of pediatricians entering fellowships for the past 5 years. It can be seen that the number is much higher in 1999–2000 than at any time in the last 5 years. At my institution, most of the 2nd year residents this year have opted for fellowship training, and I have heard the same is true at several other institutions. In my own specialty, applications for fellowship training have grown exponentially in the past 2 years. The reasons for this are not apparent, but they appear not to be economic in nature.

How will these fellowships be funded? Again I quote directly from the FOPE II recommendations (9). "Given the shortage of pediatrician-scientists, the National Institutes of Health and other federal agencies as well as foundations should develop additional mechanisms to support research fellowship training."

Where is support for research going to come in the future? Hopefully, the major source will continue to be the National Institutes of Health. Figure 1 shows a graph of data provided me by Dr. Duane Alexander of NICHD. There has been a steady increase in funding for the National Institutes of Health over the past 6 years, from $11 billion in 1995 to $17 billion in the current fiscal year, representing a 58% increase over 6 years. There is optimism that there will also be a significant increase for the next fiscal year.

WHAT IS THE FUTURE FOR PEDIATRIC ACADEMIC SOCIETIES?

To conclude then, I pose the questions: *1*) what does the future hold for the APS and other pediatric academic societies?

Table 14. *Number of pediatricians entering fellowships**

Year	No. of entry level fellows
1995–1996	728
1996–1997	717
1997–1998	664
1998–1999	684
1999–2000	796

* Data provided by Dr. J. Stockman, ABP.

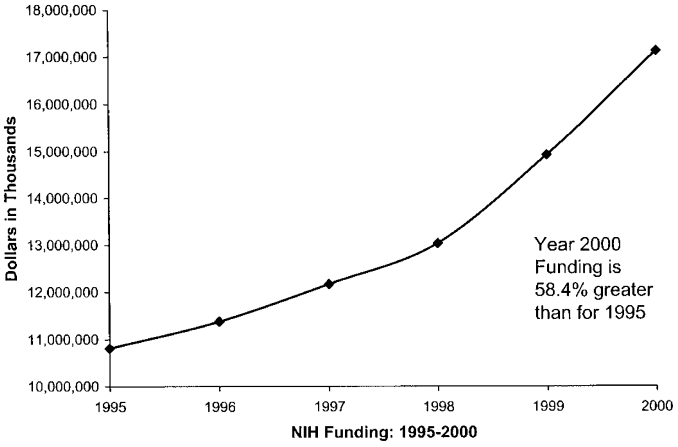

Figure 1. Funding of research (in billions of dollars) by the National Institutes of Health from 1995 through 2000.

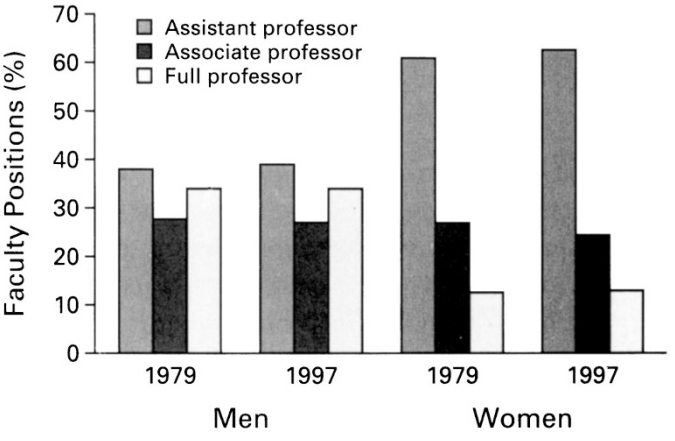

Figure 2. Distribution of men and women full time faculty positions in 1979 and 1997 according to rank. (From Moy E, Griner PF, Challoner DR, Perry DR 2000 Distribution of research awards from the National Institutes of Health among medical schools. N Engl J Med 342:250–255, Copyright © 2000, Massachusetts Medical Society. All rights reserved.)

and *2*) will they become just Neonatology/General Pediatric Societies? Strong subspecialty societies and limited travel funds are erosive factors. However, the biggest sustaining factor for the APS is that it is an organization of pediatric leaders. The biggest challenge for the membership is to help promote the recommendations of FOPE II (9). Each of you can contribute by joining the various Pediatric Workgroups started by Fred Battaglia and Dick Johnston. Several are currently wrestling with how to implement these important recommendations.

ROLE OF WOMEN IN THE FUTURE OF THE APS

On this Mother's Day weekend, it would be inappropriate for me as a woman President not to comment on the likely role of women in the future of this Society. Currently, women comprise 44% of the nation's medical school classes (11). Pediatrics has always been a specialty attractive to women, but in the past 5 years 64% to 66% of Pediatric Residents have been women. In a study by Lynn Nonnemaker published recently in the *New England Journal of Medicine*, she found that 634 more women than predicted—based on prior estimates—chose careers in academic medicine and that women were significantly more likely than men to choose such a career (12). This finding goes against the prevailing opinion that men are more likely to enter academic careers. However, the disturbing negative findings were that women continue to be far less likely to be promoted to the ranks of Associate Professor or Professor than their male colleagues, and that this did not change at all over the 19 year period from 1979 to 1997 (Fig. 2) (12). I was also dismayed to learn that only 17% of the members of the APS and 19% of the members of the SPR are women. I note that I am only the fifth woman to hold this office, in contrast to the 107 men who have served. If women are ever to be the dominant component in academic pediatrics, this all must change. On the positive side, there are currently four women on the APS Council and, in 2002, there will be another woman president.

I would like to thank you again for allowing me the privilege of serving as your President. I would also like to thank the Staff of the Pediatric Academic Societies, particularly Kathy Cannon and Debbie Anagnostelis, for the outstanding roles that they have had in organizing this meeting and for making my job easy. I would also like to acknowledge again my colleagues who provided me with information for this presentation. Finally, I would like to give very special thanks to those who have supported me throughout my academic career, including my mentors: Drs. Susan C. Dees, James B. Sidbury, Jr., and Richard S. Metzgar; and my family: my deceased parents, my husband, and my children.

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