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Science and Scholarship in Pediatrics. Presidential Address, American Pediatric Society, 1979 Annual Meeting, Atlanta, Georgia

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This is the 90th annual Presidential Address to the American Pediatric Society, and I feel a strong sense of history. I am aware that I follow a long line of scholars, scientists and activists, all of whom have had the opportunity to speak to this Society.

What can I possibly say in my own address that would bear comparison with the words of my predecessors? What new suggestions can I make? What messages can I leave?

It is difficult to be an innovator; consequently, I have chosen a theme that has concerned many before me, in our own profession and in others. I want to speak about science and scholarship, their contributions to the growth of pediatric knowledge, and the future of pediatrics as a creative endeavor. By that I mean an enterprise directed at gaining new knowledge and concerned with theories and underlying mechanisms as well as immediate applications.

As director of an institution that funds most of the pediatric and obstetric research in the United States, I feel a deep anxiety about the future of knowledge-building activities in this country, and I know that I am not alone in my concern. Within the past decade, all of us have perceived a hardening of public attitudes toward scientific research, reflected in declining fiscal support from the government and the major foundations. When we ask for explanations, we hear basic research derided as an irrelevant activity, a mere pastime for those whose sense of social responsibility is too feeble to impel them to useful action. If you care about fundamental science, the refrain goes, it follows that you do not care about society and its unsolved problems, and if you do care about society, surely you will devote yourselves directly to its welfare rather than pursue this tedious, arcane process called research.

To me, statements of this sort are very disturbing, not only because they reflect a lack of appreciation for science and scholarship, but also because they betray a dangerous ignorance of history. Many of the people who are saying these things actually imagine that they are expressing a modern and highly original vision of social priorities. However, history reveals that this clamor for immediate practical benefits at the expense of long-range scientific exploration is as old as science itself. In 1605, Sir Francis Bacon was arguing against the same philosophy in England (1):

> Even when men build any science and theory upon experiment, yet they almost always turn with premature and hasty zeal to practice not merely on account of the advantage and benefit to be derived from it, but in order to seize upon some security in a new undertaking of their not employing the remainder of their labor unprofitably, and by making themselves conspicuous, to acquire a greater name for their pursuit. Hence, like Atlanta, they leave the course to pick up the golden apple, interrupting their speed, and giving up the victory. But in the true course of experiment, and in extending it to new effects, we should imitate the Divine foresight and order; for God on the first day only created light, and assigned a whole day to that work without creating any material substance thereon. In like manner we must first, by every kind of experiment, elicit the discovery of causes and true axioms, and seek for experiments which may afford light rather than profit. Axioms, when rightly investigated and established, prepare us not for a limited but abundant practice, and bring in their train whole troops of effects.

These words were written by a man who was not an experimental scientist himself, but rather a prophet and propagandist of science, and he perceived that the choice between knowledge and practice is a false choice, based on a false dichotomy. Any society that believes it has to choose knowledge or action, research or practice is in fact accepting stagnation. Social progress arises from the interaction of a knowledge-building component that seeks to discover the underlying causes of things, and a problem-solving component that is in opposition to the practical limitations of current knowledge. These two enterprises, the ones we know in pediatrics today as research and practice, the acquisition of new knowledge and its application, stimulate each other and progress together.

Bacon saw quite clearly how this machinery of progress works, even though he lived in an age when science had barely begun to exert its full impact on the daily lives of the people. One of the most important medical discoveries of all time would be announced two decades later, in 1628, when William Harvey published his classic work, *De Motu Cordis*. Harvey's prime discovery, the circulation of the blood, was an excellent example of an axiom which brings in its train "whole troops of effects." The first effects were not salutary; Harvey became an object of public ridicule and his medical practice suffered severely. However, we all know that his eventual impact on medicine was nothing short of revolutionary.

Now one might imagine that the English-speaking world which had heard Bacon's argument for scientific inquiry, and seen the proof of its value in Harvey's work, would never again question the relevance of scientific research.

That was hardly the case, as the great French traveler Alexis de Tocqueville discovered when he visited the fledgling United States in the 1830's.

> In America the purely practical side of science is cultivated admirably... the trouble is taken about the theoretical side immediately necessary to application... But hardly anyone in the United States devotes himself to the essentially theoretical and abstract side of human knowledge. In this the Americans carry to excess a trend which can, I think, be noticed, though in a less degree, among all democratic nations (3).

The American bias in favor of practicality was so strong, de Tocqueville said, and the tradition of basic scientific inquiry was so weak, that only governmental sponsorship could provide the patronage necessary to keep the scientific enterprise alive.

And de Tocqueville issued a warning to Americans. He said that the theoretical, experimental, and applied sciences can, of course, be studied apart from one another, but, "none of them can prosper for long if entirely separated from the other two." If this separation should occur, he warned, the result would be that the wellsprings of social innovation would be stopped, and this young and vigorous America might well become as stagnant and inflexible as China under the Mandarins (3).

If these words of de Tocqueville from 150 years ago and the words of Bacon 200 years before de Tocqueville tell us anything,

it is that we are facing problems which were old even when this Society was founded. The denigration of science and scholarship and their need for defenders are not new phenomena. I think the real historical surprise is that science ever managed to achieve a foothold in the United States and that it has evolved into the vast and productive enterprise that we have today.

Those of us in this Society and particularly those of us who have been deeply involved in pediatric research should pay more heed to our own history. It can provide us with cogent arguments to counter the current fashion for immediate results. It can give us the strength that goes with our tradition, a tradition of creative response to known needs held in balance with a commitment to seek new knowledge.

That tradition was well embodied in the group who founded this Society in 1889, Job Lewis Smith, Abraham Jacobi, Thomas Morgan Rotch, Emmet Holt, Sr., and their associates. For the most part, they were not scientists. They were pediatric scholars, gifted clinical observers, dedicated teachers, and impassioned promoters of public health.

As part of their legacy to pediatrics, they have left a strong commitment to social activism. Even a cursory glance at their writings will show how appalled they were at the social conditions of 19th century urban America and the massive childhood mortality that it accepted as an ongoing natural disaster.

When Job Lewis Smith visited the squatters' huts in the area of New York City that is now Central Park, he found unmitigated squalor and a rate of infant mortality as high as that in Bangladesh today, and he refused to accept it. He did everything he could to expose those conditions, and he joined with his brother Stephen in the drive for public health legislation (4).

When Abraham Jacobi was appointed to the staff of a New York charity hospital and noticed that its rate of infant mortality was 100%, he refused to accept it. He made a public announcement of the fact and was fired because he would not keep silent (15).

When Emmet Holt, Sr., saw the number of infants dying from artificial feeding with tainted milk, he never accepted that either. He turned his own considerable investigative skills to the task of documenting the role of bacterial contamination in summer diarrhea and other fatal diseases of infancy and did his best to see that the results were brought to the attention of lawmakers (2).

These pioneers of pediatrics never limited themselves to promoting known remedies for childhood disease, and they never wanted pediatrics as a whole to follow such a narrowly defined course. All the while that they fought against preventable mortality, they were laying the philosophical groundwork for a new pediatrics based on fresh knowledge and better methods of prevention.

We can see this passion for improving the lot of mothers and children clearly demonstrated in Jacobi. He was truly the most scholarly propagandist for the new pediatrics. He was the one who laid the philosophic groundwork for a pediatric science focusing on development as its central problem, and in the process he left us with a memorable definition of our interests (6):

> Infancy and childhood are the links between conception and death, between the foetus and the adult. The latter has attained a certain degree of invariability. His physiological labor is reproduction; that of the young is both reproduction and growth. As the history of a people is not complete with the narration of its condition when established on a solid constitutional and economic basis, so is that of man, whether healthy or diseased, not limited to one period. Indeed, the most interesting time, and the one most difficult to understand, is that in which persistent development, increase, solidification, and improvement are taking place.

Pediatrics, he said, has a unique mission to study and treat the entire organism during this period of rapid development.

> I have tried to establish the claim of pediatrics to be considered a specialty. Not that it is one in the common acceptation of the term. It does not deal with a special organ, but with the entire organism at the very period which presents the most interesting features to the student of biology and medicine.
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> I have tried to prove that pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but that it has its own independent range and horizon and gives as much to general medicine as it has received from it.

When Jacobi outlined this vision of pediatrics in his Presidential Address of 1889, he was giving voice to a view shared by Smith, Rotch, Morgan and the others (2). They also were concerned with giving pediatrics a unique, knowledge-building mission because they realized that this was the only way to lift the field above mere empiricism and place it on a solid footing. As weary as they were of witnessing preventable mortality and morbidity, they looked ahead to new developmental discoveries and the new forms of prevention these would bring.

As pediatrics evolved, it acquired a strong experimental component: Gamble, Howland, Darrow, and Marriot stand out as some of the great experimentalists of the first half of this century. During their time, pediatric scientists began to acquire a strong developmental perspective, just as Jacobi had envisioned. Once advances in public hygiene and immunology had begun to contain the major epidemic diseases, the attention of investigators was drawn inexorably to the perinatal period and to developmental dysfunction. We began to focus on congenital malformations, biochemical and physiologic immaturity, behavioral and neurological disorders, mental retardation, and the early origins of adult disease, all of them developmental problems, and all of crucial importance today.

The partial solutions that we have achieved thus far carry a massive impact for public health. If we want to document that, we have only to cite the improvement in survival of premature infants over the past two decades (5).

However, we must remember that there is a great deal we do not yet know. For instance, much prematurity is still not preventable by today's methods; nor are its sequelae fully predictable. The solutions to prematurity and dozens of other pediatric problems require the same commitment to new knowledge that we had in the past and the same degree of intellectual freedom to seek it. Thus far, all of our pediatric discoveries have been made by investigators who were given time and support to follow their problems to logical conclusions, either by carrying experimental results into practice or by transferring clinical problems into the laboratory and delving into basic mechanisms.

It was that latter pathway that gave me my first experience in pediatric research. When I was working at the New York Hospital twenty-seven years ago, my mentor was Samuel Z. Levine, a former President of this Society. Levine was a brilliant teacher and an intellectual clinician. In his clinical studies, he was puzzled by the phenomenon of tyrosyluria in premature infants and wanted to know the basis for its occurrence. He found that administration of vitamin C would prevent the tyrosyluria, but he wanted to know the underlying mechanisms of the disorder and the effect of vitamin C (11). With Levine's encouragement, my coworkers and I initiated a study of the development of tyrosine metabolism in the perinatal period and found that the newborn mammal is biochemically different from the adult; the liver of the newborn and the fetus cannot oxidize tyrosine effectively (9). In fact, later work by our group and others showed that each of the nutrient-handling systems present in the normal adult has an ontogenetic history that can be traced by plotting enzyme activity as a function of developmental time (7).

These findings were fascinating to us. We no longer viewed development as an anatomical phenomenon, but rather as a fugue of enzymic activities. Some enzymes rose and some fell as the organism made the transition from fetus to infant, from the environment of water to that of air.

My coworkers and I derived immediate intellectual satisfaction from these studies. Eventually, thanks to extension of this avenue of research by us as well as other investigators, the premature

babies derived a far more tangible reward. They received formulae that were designed to fit their biochemical capabilities and to protect them from the brain damage that can accompany nutritional indiscretions. Several genetic and acquired forms of diarrhea became preventable once the development of intestinal enzymes had been studied in greater depth (8), and developmental pharmacology, a new discipline centered around the metabolism of drugs in the young, began to yield findings of therapeutic value.

Of course, I do not mean to imply that all of the advances of pediatrics in recent decades were derived from the work of persons who identified themselves as pediatric investigators. We all know that many pediatric advances have come from discoveries made outside the bounds of pediatric science, some of them so fundamental in nature that they appeared to have no immediate medical applications at the time they were made.

Consider, for example, the discovery in the early 1950's of the double helical structure of DNA. This theoretical model, a structure that could account for information coding and replication, represented an enormous intellectual breakthrough for biology. All of us found that we had acquired a new, workable mental image of the genetic material. In place of the stained clots of chromatin we had seen under the microscope and the Mendelian ratios we had learned from the geneticists, we were now able to envision this great double helix as the central thread of inheritance and evolution. All of us were intellectually thrilled by the Watson-Crick model of DNA (17).

However, we pediatricians today are even more fascinated with the therapeutic value of research on DNA. In our own institution and in many others, developmentally oriented molecular biologists are doing astonishing things with DNA. They are extracting genes and their flanking sequences from mammalian cells, cloning these stretches of DNA in bacteria or bacterial viruses, and subjecting them to direct analysis (10, 13). These cloning and splicing techniques have already been used for prenatal diagnosis of thalassemia (14), and edited versions of mammalian genes have been inserted into bacteria to create chemical factories for production of biologically active proteins. It appears certain that we will soon have large quantities of human insulin available for therapeutic purposes (16). It is also quite possible that sizeable quantities of pituitary growth hormone can be obtained for research purposes and for treatment of pituitary dwarfism (12).

That is not all. If basic research is allowed to continue, there is great hope that direct study of natural gene clones will yield information on the "on and off" switches of the mammalian gene. Once we know how to turn genes on and off, the possibilities for medical application of this knowledge are endless. Perhaps future pediatricians will be able to reactivate the gene for fetal hemoglobin in the child with sickle-cell anemia, regulate neurotransmitter synthesis in certain biochemical disorders of the brain, or control the steroid receptors and hormone-activated genes that play a role in so many endocrine disorders.

Here I am speaking of the pediatrics of the future. It has not arrived yet, but its clientele has. Every year thousands upon thousands of children are killed or crippled by disorders that we have not the knowledge to treat or the wisdom to prevent. We must acquire this knowledge. Promoting the growth of knowledge along with promoting health has been our traditional role as members of this Society.

I want to see the fundamental scientists in this audience continue with their work; it has been the mainspring of pediatric progress for the past 100 years. I would like the clinical investigators who make up the bulk of the pediatric research establishment to have the same options that I did 25 years ago: to carry their studies in the direction dictated by logic, either toward wider application or toward more basic investigation of mechanisms. I would hope especially that chairmen of academic departments would refuse to be intimidated by fiscal stringencies and pressure from administrative authorities but rather would continue vigorously their historic role of nurturing research and maintaining a climate in which it can flourish. Most of all, I would like practitioners to carry to their patients a growing and evolving pediatric science, one that offers hope of new discoveries along with known therapies and that bases its preventive advice on a firm understanding of behavioral and biomedical mechanisms.

Yet I know that all of my hopes for the future of pediatrics are now threatened by the same short-sighted pragmatism that Alexis de Tocqueville warned us about 150 years ago. It has crept into the universities as well as the corridors of government and has now become so entrenched that is is not likely to be removed by action in those arenas alone. If we want to loosen its hold, our only hope is direct appeal to the public to make the public aware of the importance of new knowledge to their well-being. We in this Society must remain true to our heritage and become public advocates for science and scholarship. We must join forces with those in other disciplines who are trying to keep the scientific enterprise alive because it is all science that is threatened today, not just pediatric research.

Of course, if we become strong advocates for basic research, we will be accused of elitism and naivete. However, it seems to me that there is something worse than being condemned as naive elitists. The possibility remains that we may condemn ourselves and the children we serve to a loss of hope. If we fail to maintain pediatric science, the results will be tragic for all of us, fundamental scientists, basic and applied clinical researchers, practitioners, and most of all for children. All of us may find ourselves the heirs of a fragmented, dispirited, and stagnant discipline that perpetuates misinformation and iatrogenic disease along with ill-understood cures, generation unto generation.

We must remember that of all the major branches of science from theoretical physics to sociology, ours is the only one that is specifically focused upon infants and children and the adults they will become. We must contribute our unique perspective to the current debate on the value of science. We may do well to remind our fellow citizens of Alexis de Tocqueville's warning to Americans, issued so many years ago: "Some peoples may let the torch be snatched from their hands," he said, "but others stamp it out themselves"(3). It is our choice.

REFERENCES AND NOTES

1. Bacon, F.: Novum Organum. In: R. M. Hutchins: Great Books of the Western World. p. 105 (Encyclopedia Britannica, Inc., Chicago, 1952).
2. Blackfan, K. D.: Past presidents of the American Pediatric Society, 1888–1938. Am. J. Dis. Child., *56:* 1 (1938).
3. de Tocqueville, A.: Democracy in America. (Doubleday, New York, 1969).
4. Faber, H. K.: Job Lewis Smith, forgotten pioneer. J. Pediatr., *63:* 794 (1962).
5. Forbes, G. B.: Pediatrics. J. Am. Med. Assoc., *239:* 522 (1963).
6. Jacobi, A.: Collectanea Jacobi: Collected Essays, Addresses, Scientific Papers and Miscellaneous Writings, Vol. 1. (The Critic and Guide Company, New York, 1909).
7. Kretchmer, N.: Developmental biochemistry a relevant endeavor. Pediatrics, *46:* 175 (1970).
8. Kretchmer, N.: Biology of carbohydrate intolerance. In: R. Suskind: Textbook on Pediatric Nutrition. (Raven Press, New York, 1980) (in press).
9. Kretchmer, N., Levine, S. Z., McNamara, H., and Barnett, H. L.: Certain aspects of tyrosine metabolism in the young. I. The development of tyrosine oxidizing system in human liver. J. Clin. Invest., *35:* 236 (1956).
10. Leder, P., Tilghman, S. M., Tiemeier, D. C., Polsky, F. I., Seidman, J. G., Edgell, M. H., Enquist, L. W., Leder, A., and Norman, B.: The cloning of mouse globin and surrounding gene sequences in bacteriophage. Cold Spring Harbor Symp. Quant. Biol., *42:* 915 (1978).
11. Levine, S. Z.: Tyrosine and phenylalanine metabolism in infants and the role of vitamin C. In: The Harvey Lectures. Series 42, 1946–1947, p. 303 (Academic Press, Inc., New York, 1947).
12. Martial, J. A., Hallewell, R. A., Baxter, J. D., and Goodman, H. M.: Human growth hormone: complementary DNA cloning and expression in bacteria. Science (Wash. D. C.), *205:* 602 (1979).
13. O'Malley, B. W., Roop, D. R., Lai, E. C., Nordstrom, J. L., Catterall, J. D., Swaneck, G. E., Colbert, D. A., Tsai, J. M., Cugaiczyk, A., and Woo, S. L. C.: The ovalbumin gene: organization, structure, transcription and regulation recent progress in hormone research. In: R. O. Greep: Proceedings of the Laurentian Company Hormone Conference. Vol. 35, p. 1 (Academic Press, Inc. New York, 1979).
14. Orkin, S. H., Alter, B. P., Altay, C., Mahoney, M. J., Lazarus, H., Hobbins, J. C., and Nathan, D. G.: Application of endonuclease mapping to the analysis and prenatal diagnosis of thalassemias caused by globin-gene deletion. N. Engl. J. Med., *299:* 166 (1978).

15. Truax, R.: The Doctors Jacobi (Little, Brown and Co., Boston, 1952).
16. Ullrich, A., Shine, J., Chirgwen, J., Pictet, R., Tischer, E., Rutter, W., and Goodman, H.: Rat insulin genes: construction of plasmids containing the coding sequences. Science (Wash. D. C.), *196:* 1313 (1977).
17. Watson, J. D., and Crick, F. H. C.: A structure for deoxyribose nucleic acids. Nature (Lond.), *171:* 737 (1953).
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