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REVIEW FOR THE SHEIKH HAMDAN BIN RASHID AL MAKTOUM AWARD FOR MEDICAL SCIENCES

Comments on the past and predictions on the future of neonatal research – consortia, randomized cluster trials, brain care centres and xenon

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Abstract

I will discuss the background of how ideas for research projects evolve. This is a topic that researchers rarely explain. It is obviously very important. Unfortunately, editors rarely, if ever, request that such material be included in publications. My friend, Dr Mary Ellen Avery, Professor at Harvard University, suggested the subject to me and intended to write such an article herself. Unfortunately, she never did. I will discuss the birth of three good ideas I have had over a long career in neonatology, from 1952 to 2011! These were phototherapy, the Vermont Oxford Network and helping to organize large, international randomized control trials of xenon. I am now 85 years old, long past the age you are supposed to have 'hot' ideas, but I think I have important ideas about the future. It is my belief that brain care, brain cooling plus some other agents are the future. Proving this, however, will take reorganization of our current ways of carrying out clinical research. It is my personal belief, based on the basic research to date, that xenon gas is likely to be successful. To prove this 'idea', our field needs to reorganize into large consortia. It will probably take a decade or longer to prove this hypothesis by carrying out the necessary, very large, randomized trials. We need to encourage neonatologists to unite and work together on new advances.

Comments on the past and predictions on the future

Where do new ideas come from? After over 35 years as editor of *Pediatrics*, reading thousands of articles, I cannot remember one in which the authors explained how or where they got the idea to study something really new.

I would like to give you some insights into why I did some of the things I did in my career that turned out to be worthwhile.

Phototherapy

I was an avid read of the *Lancet*. I was a young assistant professor at the University of Vermont. I read Dr Cremer's article on light and hyperbilirubinaemia.[1] I was not impressed. I ignored it. It seemed absurd. It was not a controlled study. Ten years later I realized that phototherapy was being used in France, Chile, Uruguay and Italy without any controlled trials having been carried out! Dr Mario Ferreiro and I carried out a small controlled trial that showed that phototherapy is indeed effective.[2] I spent the next 10 years defending its use. Finally, a very large randomized trial was conducted by the National Institute of Child Health and Human Development (NICHD)[3] proving phototherapy is effective in avoiding exchange transfusions. It took a very long time, 10 years, and lots of anguish to defend this new therapy.

Vermont Oxford Network

During my time as a resident at Columbia Presbyterian Medical Center (1953–55), residents were required to formally present ideas to Professor R McIntosh, chairman of the department. It was a very important part of our training. I had worked in the two other premature centres in New York City (Cornell, Bellevue), and both believed that they had

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the best results (in terms of survivors) in the USA. I had gathered the survival statistics from the other hospitals. My presentation was roundly criticized by Drs McIntosh, W Silverman and R Day. These men were giants in the field. I was crushed and humiliated. I had not considered a number of factors that could impact on my results. Forty-five years later, I had not given up the idea of being able to compare clinical results in neonatal intensive care nurseries. I spent a sabbatical in Oxford, England, in 1975, where I met Sir Ian Chalmers and learned about the new National Epidemiology Unit. I realized that neonatologists in England were interested and willing to join together to carry out randomized trials. It was a great idea. We have since worked together whenever possible.

Subsequently, I placed an advertisement in *Pediatrics* inviting interested neonatologists to form a network that would facilitate meaningful comparisons among institutions. Forty-four neonatal nurseries joined the network in 1980. Drs Jeffrey Horbar and Roger Soll organized the network well. Under their leadership, it achieved 850 members and has published many articles.[3] It is the largest neonatal database in the world. It has proved to be invaluable in quality improvement studies.

Tracheal aspirate surfactant and Dr T Fujiwara of Japan

Dr Mary Ellen Avery and I were good friends. We both trained under D Clement Smith at Harvard in 1956–7. She chose to study 'sweat' with Dr J Meade. I did not think it was a great choice. She was right, of course. It was the beginning of the surfactant era of research, which changed forever the treatment of respiratory distress syndrome.

I read an article in *The Lancet* by Dr Fujiwara of Japan,[4] describing a small trial of tracheal aspirate surfactant in 10 infants. I was impressed and excited. I invited Dr Fujiwara to an American Academy of Pediatrics (AAP) meeting to present his findings. However, the audience was not very impressed. He was depressed. I was excited and enthusiastic. So was Mary Ellen, but she did not want to have anything to do with future clinical trials or the commercial development. 'It's not my field of interest!'.

I went to Japan to visit Dr Fujiwara. I watched him pour a milky white fluid into the trachea of a very sick, blue infant with respiratory distress syndrome. Five minutes later he was pink! I was very, very impressed. Dr Fujiwara offered to give me a supply of tracheal aspirate surfactant, which we shared with Taeusch of Harvard for a clinical trial.[5] I contacted Mr Dewey Sehring of Ross Laboratories, which had purchased the right to develop a product and named it Survanta. I predicted we could carry out the trials and get Food and Drug Administration (FDA) approval in 4–5 years. It took 9 years.

A new era begins: brain cooling

The early history of brain cooling is well summarized by Dr D Edwards and DV Azzopandi.[6,7] This therapy is based on a substantial amount of solid basic laboratory evidence along with extensive small and large animal studies,[6] studies that took place over a 20-year period.

Brain and mild body hypothermia was tested in 11 randomized trials with positive results. Cooling increases infant survival (reduction in mortality of 5%) and reduces the chances of having neurodevelopment delay at 18 months of age by about 15%.[6] Recent evidence in long-term survivors indicates that these positive results remain at 7 years of age.[8]

What's the next step?

The NICHD has launched a series of three trials to answer important clinical questions about the optimal duration and timing of cooling. These trials will last at least 3–4 years. The results are important because, before we launch new therapies to be added to cooling, we should have standardized cooling therapy.

Potential problems ahead

It is likely that over the next few years neonatologists will add various drugs to brain-cooled patients. The result will be, at best, many uncontrolled, small studies the results of which cannot be interpreted. Nearly all of these will be of drugs not approved by the FDA.

The future of funding for research – consortia

Economic conditions in the USA are likely to result in decreased funding for all clinical research.

The government and industry are well aware of this future problem. They are encouraging the development of consortia. Consortia groups of

organizations such as academic institutions and industrial enterprises are working together to achieve common goals, for example developing a new treatment. Their funding is derived from industry, medical research groups, private foundations and parents/patients. Governments may fund the consortium's operating expenses. The FDA and industrial organizations have to date funded some groups.

Cluster trials – preferable in some countries

All new therapies for brain care will require large randomized control trials. It is unlikely that many neonatal units will not want to participate in standard randomized trials. However, in many countries, randomized controlled trials are not favoured.

I would therefore expect that parents and physicians would be much more likely to join a cluster design trial. In this model, the whole care unit chooses one therapy for all its patients and units are randomized by hospital unit.

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