2022 William A. Silverman Lecture
Where's the Evidence?

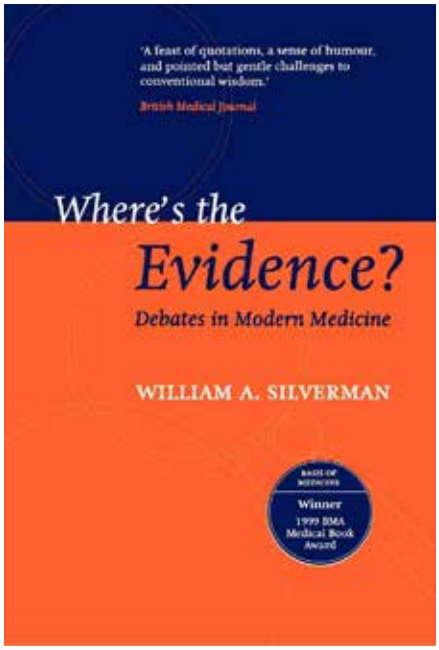
Haresh Kirpalani MD, MSc

Hello. Good afternoon, everyone. First of all, I really want to thank the Section of Neonatal and Perinatal Pediatric Medicine of the AAP and its current Chair, Dr. Lily Lou.

Lily, thank you for the very kind words. Although I'm not physically present at the meeting, she told me what she was going to say. And I'm very touched. I must apologise to both her, to Dr. Silverman, and the whole committee of the perinatal section of the AAP, and to the audience for not being there. I gauged that with my age and my prior asthma that I was over the baseline risk for consequences from COVID. That made it uncomfortable. I think perhaps Dr. Silverman might approve of my attempt at risk stratification. But I want to thank the committee again. I'm very humbled and very conscious of Dr. Silverman's contribution, and this was beyond my expectation.

"This book consists of essays that he wrote under either a 'nom-de-guerre' or 'nom-de-plume.' I'm not sure which title Dr. Silverman would prefer, but he signed himself "Malcontent" when he originally wrote these essays entitled as "Fumes from the Spleen." "

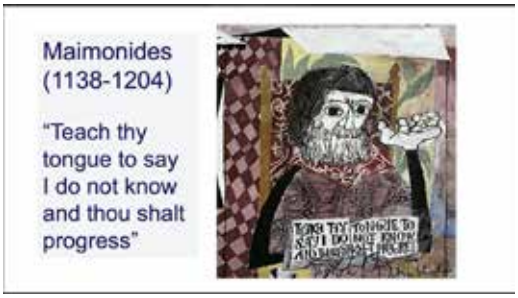
I think it's appropriate to begin with some small vignettes about Dr. Silverman. Even though most of the audience most likely full well know about Dr. Silverman. The title of my talk, "Where's the Evidence?" comes from his book shown here, *Where's the Evidence? Debates in Modern Medicine* (1).



This book consists of essays that he wrote under either a 'nom-de-guerre' or 'nom-de-plume.' I'm not sure which title Dr. Silverman would prefer, but he signed himself "Malcontent" when he originally wrote these essays entitled as "Fumes from the Spleen." He wrote these after he stepped down early from the chair at Columbia. And the reason he stepped down, I think, is quite interesting. He stepped down, he said, because he had become so disillusioned with how people use data from physiological laboratory studies to treat premature babies.

"So what was Dr. Silverman's mission?...'If we respect truth, we must search for it by persistently searching for our errors.'"

So what was Dr. Silverman's mission? I believe that the quotes that he himself used either in his prefaces or in the bodies of his works give us some measure of the man. Here is what he wrote at the end of his preface to a book where he cited Karl Popper, the famous philosopher of science, saying, "If we respect truth, we must search for it by persistently searching for our errors." And that was certainly one leitmotif of Dr. Silverman, one that prompted his friends to commission a piece of art. It was a picture of the Spanish Jewish philosopher, physician Maimonides, of the 12th century. And one of his sayings is depicted on this tablet, "Teach Thine tongue to say, I do not know, and thou shalt progress."



And indeed, Silverman would often cite this. Now, all of this sounds extremely serious. And he was a very serious man. But that doesn't mean to say Dr.Silverman didn't have his moments of mischief. For example, he would insist everyone distrust authority. And when visitors came to his unit in Columbia, he would hand them a badge. And the badge, which he would ask them to wear, would be said—and forgive me, I know no Latin—but it would say "Semper Plangere." (2) Apparently, that means "always complain." Now, despite those mischievous comments, you can see the undertone here. This was that he distrusted prescriptions that were not based on evidence in medicine.

First of all, I should say that I have no financial relationship to disclose or conflicts of interest to resolve. I will also not discuss any unapproved or off-label drug use.

In the next 25 minutes, I will try and discuss some questions or examples that Silverman gave us from which we can profit and learn. And, I'm going to try and explore them in today's context. My outline is as follows: I'll first highlight two questions posed by Dr. Silverman in relation to choosing therapies. He said that

we should always consider the difference between association and causation. Thus, one question he posed was "Is association always causative?" In my view, another question he raised for our attention was "Is the whole notion of all physiological arguments sufficient to warrant a course of therapy?"

I'll then examine these questions using selected neonatal examples to highlight some categories that were used by Dr. Silverman. In addition, I ask how long did it take from the physiological postulate that was raised before the randomised controlled trial, or RCT, verification or refutation of that postulate?

The first question that Dr.Silverman posed to remind us of is the difference between association and causation. This graph (Figure 1) is drawn from his famous book, *Retrolental Fibroplasia—a Modern Parable* (3). We now know that disease as Retinopathy of Prematurity. On the X-axis are the years from 1938 through to 1946, and the solid black line on the Y-axis is the incidence of Retrolental fibroplasia (RLF). This is the same disease we know as Retinopathy of Prematurity. You see the horrifying spike as neonatal intensive care took hold.

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Around the same time, you also see the rise in three therapies, inhaled oxygen, water-soluble vitamins, and iron. Now, at the time, people came to a premature conclusion that iron was the causative agent in RLF by extrapolating from its physiological relationship to vitamin E. But as we now know, the culprit was actually oxygen. Clearly, iron was only an association.

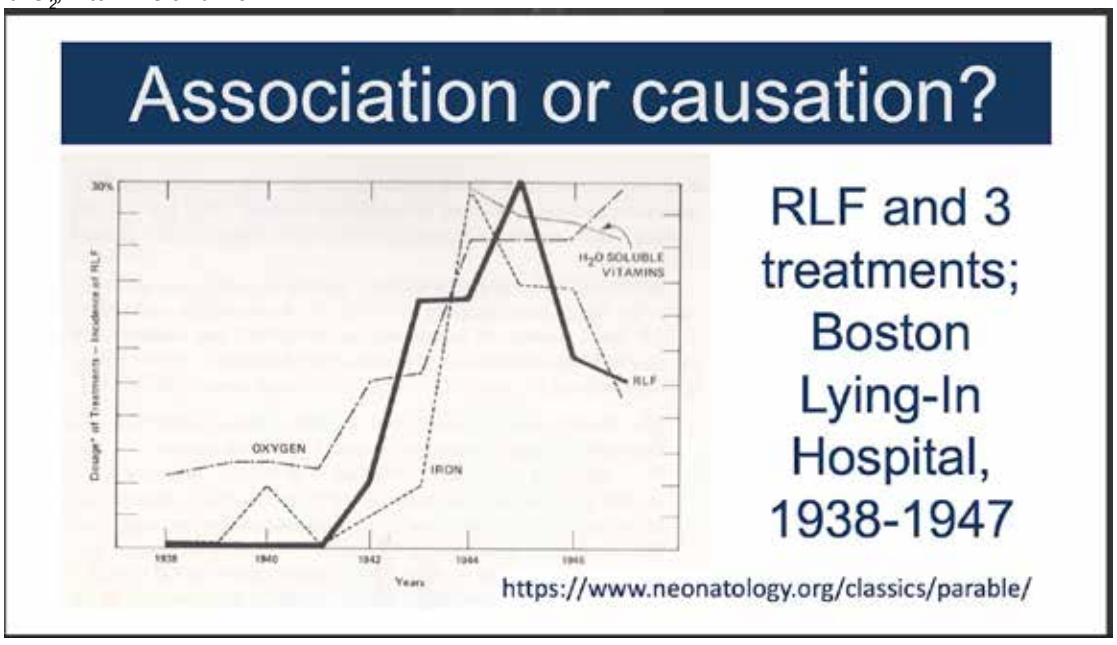
"You see the horrifying spike (in ROP) as neonatal intensive care took hold. Around the same time, you also see the rise in three therapies, inhaled oxygen, water-soluble vitamins, and iron. Now, at the time, people came to a premature conclusion that iron was the causative agent in RLF by extrapolating from its physiological relationship to vitamin E. But as we now know, the culprit was actually oxygen. Clearly, iron was only an association.""

The second question I'm going to take from Silverman as a model for us is whether physiology is sufficient to warrant a line of therapy. This quotation comes directly from his book on RLF, where he records what he wrote in a baby's chart the following:

"It has been decided to try ACTH (Adrenocorticotropic Hormone). On the rationale that 1) it is a connective tissue disease; 2) prematures are maybe deficient in ACTH; and 3) no other agent has given any indication of beneficial effect." (4)

You can hear the note of anxiety about writing this in the chart. I think we can see the dilemma that he was in as the physician of this baby. He wrote about his patient that she was:

Figure 1. RLF and O_2, vitamins and Fe



"the prematurely born daughter of (a colleague)…after six miscarriages. (This infant) proceeded to 29 weeks…following definite signs of RLF...the treatment was started more in desperation than conviction."

Her eyes were "almost normal" when she was sent home. Now, the story did't end there while this was a satisfactory ending, of course, for this child and this family. But "we were puzzled about two infants" who recovered without treatment.

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I think all of us have, at times, been in such a dilemma, and as physicians, we recognise this dynamic. But the quandary was posed to him, and the experience led him to do a randomised trial. In that randomised trial, ACTH was found to be ineffective. This was a "parable," in his words, and in a nutshell, the story behind his most famous book. This copy on my slide looks a bit battered. It's quite old and was lent out on several occasions, but thankfully the whole book now is available free of charge at the website *https://www.neonatology.org/classics/parable/*. I strongly urge particularly young people who don't know about Silverman to read this book. It reads like a detective story.

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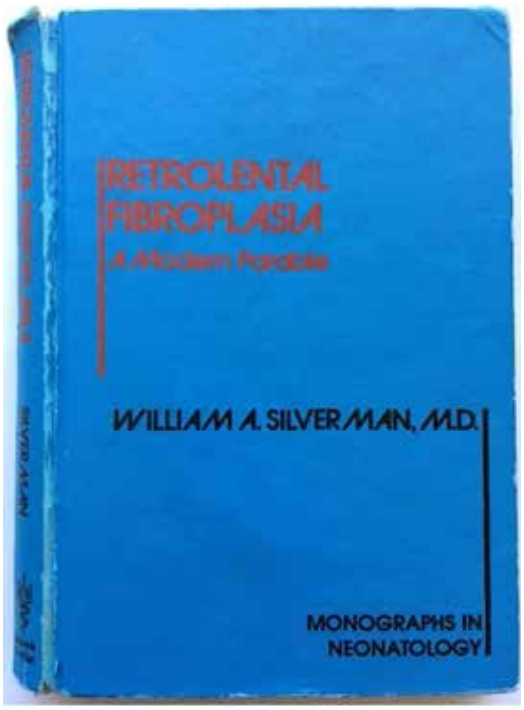

Figure 2. Results of some "Proclaimed" Therapies in the Development of Perinatal Medicine

Gradual Changes in Therapy	Consequences* Led to Sounder Practice	Led to Disaster	Misled into Fruitless Byways
Testosterone to stimulate growth of prematures		?	
Thyroid hormone . . ibid . . .			×
DES to prevent miscarriage		×	
Progestins to prevent miscarriage		×	
Exchange transfusion	×		
Supplemental oxygen for periodic breathing		×	
Initial thirsting and starving		× (?)	
Synthetic vitamin K prophylaxis		×	
Low-fat, high-protein feedings		?	
Sulfisoxazole prophylaxis		×	
Chloramphenicol prophylaxis		×	
Gastric emptying to prevent RDS**			×
Sternal traction for RDS			×

"The example that I picked to illustrate 'disaster' was oxygen for periodic breathing. As you can see..., certainly unrestricted oxygen ablated the periodic breathing seen in air and led to a more regular breathing. But as Silverman pointed out, unrestricted oxygen had led to harm or disaster with retinopathy."

He placed his thoughts about proclaimed therapies in a very famous table, which showed three categories about various "putative therapies." (5) I've expanded that in the next slide (Figure 2) to emphasise that sometimes the physiology-based intervention led to "sounder practice" or to "disaster" or to "fruitless byways."

Here is one example for each of these categories from Silverman's famous table. The first was CPAP (continuous positive airway pressure) for RDS, showing a picture of one of the babies in Dr. Gregory's first cohort in 1971. (6) At the time that Silverman wrote the book, he still placed a question mark by CPAP, although he thought this had led to sound the practice. It took until 2008 before Colin Morley published the COIN trial (7) and shortly after Neil Finer and Wally Carlo (8) evaluated the benefits of CPAP in a much more systematic way to avert intubation.

The example that I picked to illustrate "disaster" was oxygen for periodic breathing. As you can see in the slide, certainly unrestricted oxygen ablated the periodic breathing seen in air and led to a more regular breathing. But as Silverman pointed out, unrestricted oxygen had led to harm or disaster with retinopathy.

Finally, the example I've chosen from Silverman as being a fruitless byway is sternal traction. And you can see there that there's a stitch under the surface sternum moving up to some weights, which counter-balances the tendency of the chest wall to collapse the very compliant preterm chest wall. This was supposed to avert a sternal and pulmonary collapse. Of course, it didn't work but didn't overtly lead to harm except perhaps the pain. And this was a "fruitless byway."

What about in a more modern era? I'm going to depict an example for each of the three of these categories. In the first example, I've asked if randomised controlled trials (RCT) verified that indeed the intervention had led to sound practice.

This was the case for inhaled nitric oxide for term infants with persistent pulmonary hypertension of the newborn. And in fact, the gap here from hypothesis to RCT verification or refutation was rather short and accomplished in ten years. This slide (Figure 3) shows four gentlemen at the top and relates a rather controversial story because the three gentlemen on the left were acknowledged by the Nobel Prize. Dr. Moncada on the right, although he had participated in all of the same work and had developed the story of nitric oxide, he was not so credited. But in a poetic form of justice perhaps, his article (9) is probably far more quoted than the articles by the Nobel Prize winners. So perhaps a small justice for Moncada. Or perhaps the message here is that the merit lies in the work itself without any consideration of prizes.

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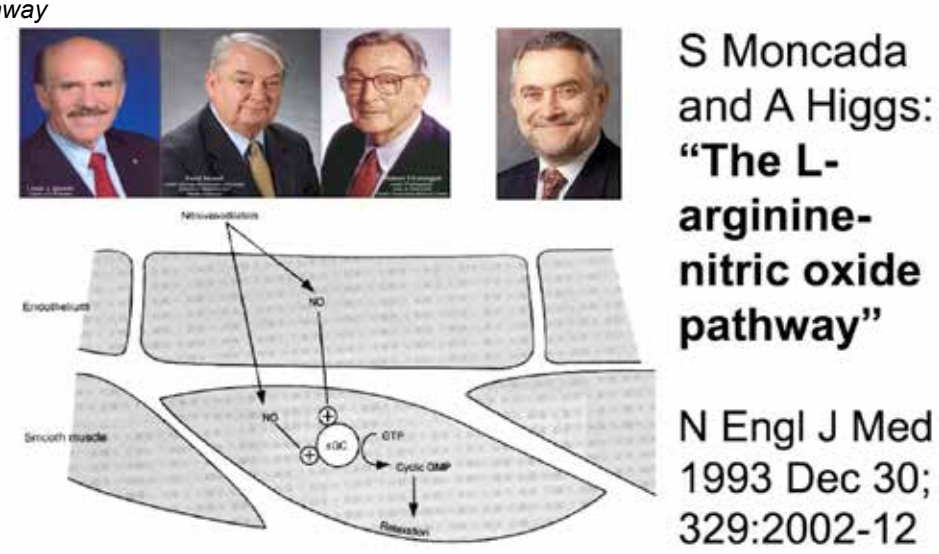
These gentlemen had collectively displayed that in order for vasodilators to exert a relaxation of smooth muscles and arterial vessels in all the vascular compartments of the body, the endothelium was a necessary component. Because it elaborated what they called the endogenous relaxation factor, or the RF, this was later shown to be nitric oxide, which diffused from the endothelium to the smooth muscle cells, where through the cyclic

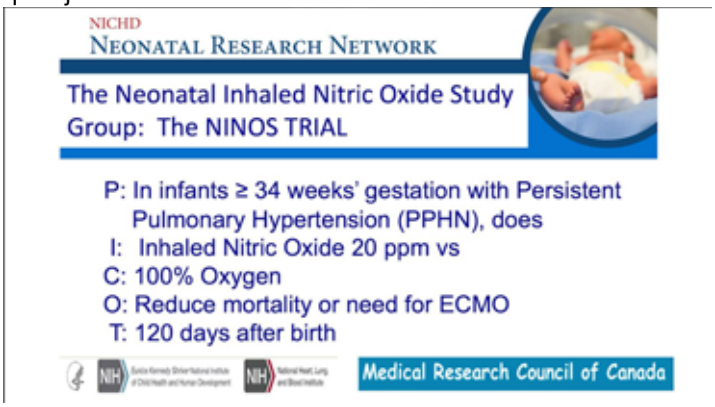
Figure 3. The Nitric Oxide Pathway



GMP pathway, it induced relaxation.

Very quickly, our colleagues in the 1990s extrapolated this to infants in observational studies. Dr. Neil Finer in Canada obtained funding from the Medical Research Council of Canada and initiated a trial. Very shortly thereafter, the Neonatal Research Network in the USA, with Richard Ehrenkrantz and Linda Wright, joined the NINOS trial.

That asked this question: "In a population of infants who are greater than 34 weeks gestational age with PPHN (persistent pulmonary hypertension), does inhaled nitric oxide (NO) at 20 parts, as opposed to a control of 100% oxygen, reduce the outcome of mortality or the need for ECMO (Extracorporeal Membrane Oxygenation), by 120 days after birth?" Neil and Richard showed their results of their trial in 1997 (10). I was very fortunate that Neil had put me on the executive committee of that trial when I was quite junior.



The primary composite outcome was convincingly positive for inhaled NO. Death or ECMO was reduced from the Control group rate (77/121 [63.6%]) with inhaled NO (52/114 [45.6%], p=0.006). The trial was closed early for benefit, but only about 20 babies away from target sample size. This cohort of infants with hypoxic respiratory failure had not responded to aggressive conventional therapy. But, as you can see, if we separate out the components of the primary outcome, there was no reduction in death alone.

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My second example is in the category of "disaster" or harm and sustained inflation (SI) at birth for extremely preterm infants who have a poor respiratory effort. I believe that you can trace the gap from hypothesis to randomised trial verification or refutation to just under 40 years. The story starts in Nottingham, England, where the group of Dr. Milner with Dr. Vyas displayed that babies requiring resuscitation could establish a functional residual capacity quicker if a sustained inflation of about 5 seconds, as opposed to the standard inflation time, usually less than one second. That was regardless of either a slow waveform, a square wave, or a slow rising form. (11)

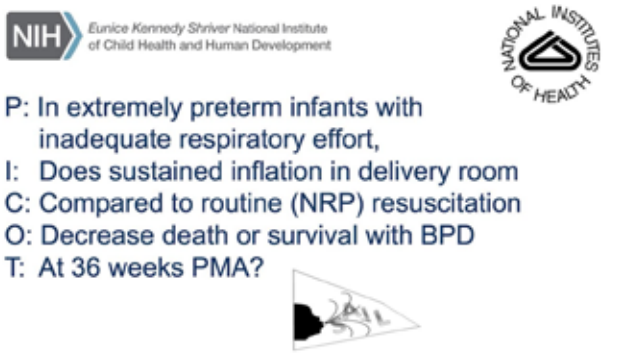
It took a few years, but in the 2000s, the group, led by Stuart Hooper in Melbourne, explored this further, using a slightly longer sustained inflation using a synchrotron. (12) A synchrotron is simply an X-ray where the subject is placed an extremely long way away from the X-ray generation plant. This narrows the X-rays into a parallel beam to you give extremely high resolution. What I want to show you are two videos of rabbit pups from the above paper by Dr. te Pas. The first is of a rabbit pup trying to establish a spontaneous breath. You can see the rabbit pup is breathing and does open the main conducting airway opening, but the lung itself is only minimally opening.

If we move over to the second video, a sustained inflation of about 20 seconds was delivered to this rabbit pup through an endotracheal tube. Now the same initial pattern with the conducting airways opening is seen. However, then you see this beautiful appearance of small round circles coalescing into the lung. Now the rabbit is performing its own respiratory manoeuvres. The difference is very vivid.

"This was extrapolated into human physiology and further extrapolated away from using an endotracheal tube. That was because, by this stage, we knew that intubation was not good. So people were trying to avoid this and tried to deliver sustained inflation with a mask. And some smaller trials were done that indicated some benefit.."

This was extrapolated into human physiology and further extrapolated away from using an endotracheal tube. That was because, by this stage, we knew that intubation was not good. So people were trying to avoid this and tried to deliver sustained inflation with a mask. And some smaller trials were done that indicated some benefit. Two in particular led by Arjan Te Pas in Holland (13) and another led by Dr. Lista in Italy (14). However, the benefits that were being described were short-term.

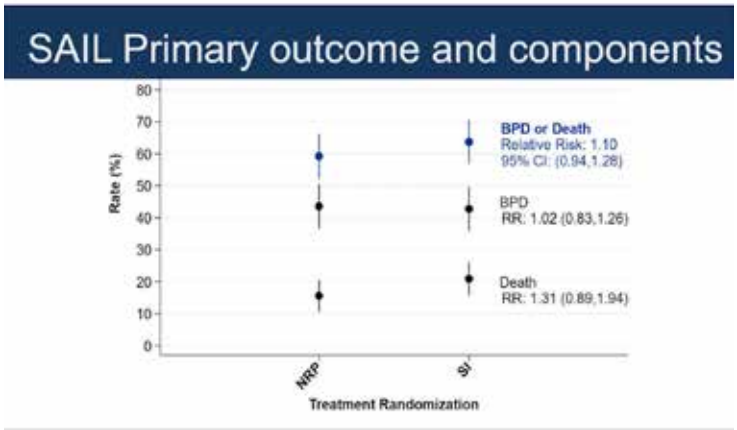
Nobody had yet asked in an adequately sized trial this primary PICOT (patient, intervention, comparison, outcome and time) question: "In a population of extremely preterm infants with inadequate respiratory effort, does sustained inflation in the delivery room as compared to a control arm of routine (or neonatal



resuscitation program, NRP) control resuscitation decrease the outcome of death or survival with BPD (bronchopulmonary dysplasia) at 36 weeks postmenstrual age?"

A group of international workers combined forces to answer that question. We calculated a sample size of about 600 babies was needed to answer that question (15). The primary outcome of death or BPD, when the trial was stopped on the Y axis, was no different (RR 1.10 [95%CI 0.94, 1.28]).

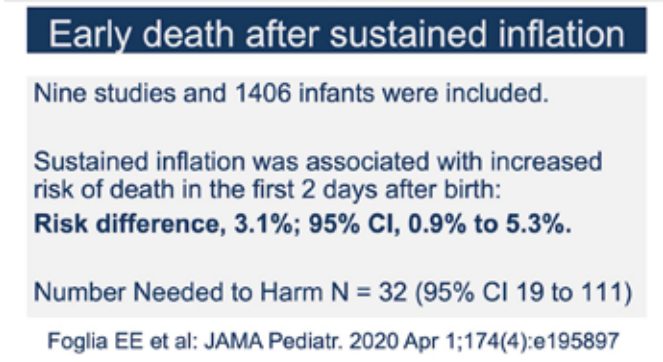
Figure 4. Sustained Inflation Outcome



When examined by either BPD or death alone, there still was no difference. Now I said that the sample size was 600, but the trial was prematurely stopped at just over 400. It was stopped after the independent DSMB (Data and Safety Monitoring Board), led by Dr. A. Jobe, had reviewed the data up to 400 babies.

When we designed the trial, we were careful to ensure to pick up signals of harm. One signal we were looking for was early death. That is death within the first two days of life. There was an excess mortality in the sustained inflation group (adjusted risk difference 5.6 [2.1, 9.1]).

Figure 5. Early Death After Sustained Inflation



But because the trial was stopped early, correctly, I would argue there remained a potential for bias. To that end, we were fortunate that Foglia conducted a meta-analysis including about 1400 babies. (16) That analysis confirmed that sustained inflation was associated with an increased risk of death in the first two days of after birth (Figure 5). The risk differences shown the number needed to harm was a mean of 32, with a 95% confidence interval of 19 to about 111.

This was important because the practice of sustained inflation was passing into a standard of care in several parts of the world, particularly, I think it's fair to say, in Europe. So before this became a much more generalised therapy, at least we indicated some evidence to suggest SI required more study before entering standard practice.

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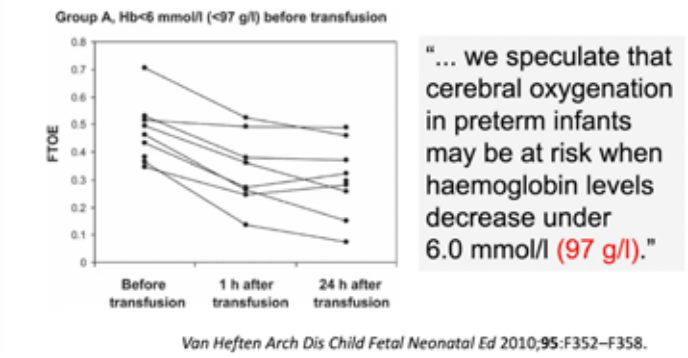
The last example I'm going to suggest—following Silverman's paradigm—is one where RCTs suggested a "fruitless byway." This example is on the notion of a liberal red blood cell (RBC) transfusion strategy with higher hemoglobins will improve brain development in preterm infants. Here the interval from hypothesis to RCT was actually just over 40 years. I submit the story can be traced to the late 1970s. This is illustrated by this quote from some authoritative workers: "We have demonstrated a highly physiological phenomenon, a defect in oxygen supply which correlates with the clinical syndrome of anaemia, most commonly seen an incidence of shorter gestation. This occurs during the period of maximum brain growth and could prejudice the child's chances of achieving full potential later in life." (17)

Some small studies tried to evaluate this, but not very many in a randomised way. However, newer observational data led to indirect support for the above statement. This shows data from the newer technology of near-infrared spectroscopy, or NIRoscopy, for cerebral oxygenation (18). This graph (Figure 6) shows the fractional oxygen extraction (FTOE) of blood from the brain before, immediately after, and 24 hours after transfusion. I draw your attention to the haemoglobin level at which these babies were transfused, of 97 grams per litre (9.7 grams per decilitre). There was a decrease after RBC transfusion in the FTOE. The authors speculated that cerebral oxygenation and preterm may be at risk when haemoglobin levels decrease under 97 grams per litre.

Figure 6. Effect of RBC Transfusion on FTOE



As I say, there were some randomised studies looking at this, but they were relatively small. It's only recently that two large

studies were able to address this question, and that included the Transfusion of Prematurity (TOP) trial conducted by the Neonatal Research Network (NRN) of the NICHD (19); and also a German network trial led by Dr. Axel Franz (20).

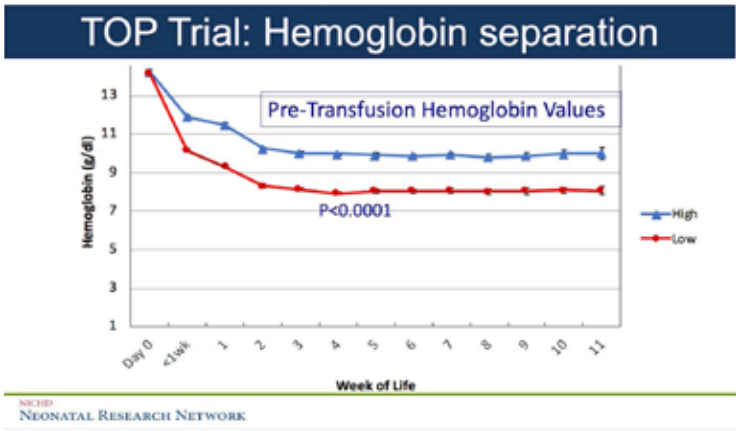
Both trials asked the following PICOT question:

"In ELBW (extremely low birthweight) infants, does randomisation to a liberal RBC transfusion strategy—as compared to a restrictive RBC transfusion strategy—show a reduced death or impairment at 22-24 months corrected age?" The largest trial was the TOP trial.

This summary (Figure 7) displays haemoglobin levels in infants by randomised group in grams per decilitre.

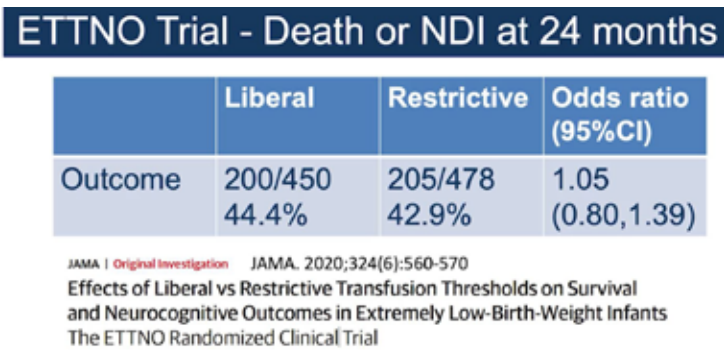
Figure 7. Haemoglobin Levels in Infants

Haemoglobin was about two grams per decilitre higher in the



liberal transfusion strategy group above infants randomised to the low arm, and that difference was maintained through hospital stay. Importantly that level in the high group was above that speculative level of 9.7 grams per decilitre we noted earlier. However, at two years of outcome, the total primary outcome of death, or MDI, in the population with 93% follow-up showed no difference (RR 1.00 [95% CI 0.92, 1.10]). It's always good to have replicated data. The German group had reported just a month before we did, and although a smaller study, had almost exactly the same findings (OR 1.05 [95%CI 0.80, 1.39]). So I think we can be confident that transfusing infants to a high transfusion level within the ranges of the top algorithm does not confer benefits for death or long-term neurodevelopmental outcome.

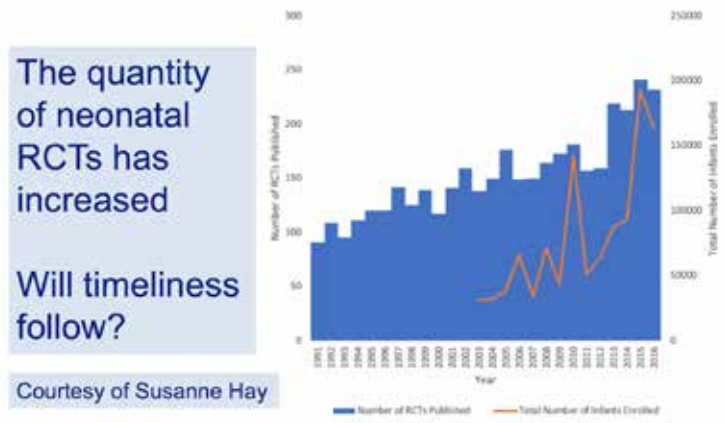
Figure 8. Outcome of Liberal v. Restrictive RBC Transfusion



Now, I think I've displayed (to) you that the three categories that Silverman used are still pertinent, but perhaps I may have been a bit gloomy. I've suggested that we're being rather slow. Perhaps I shouldn't be so gloomy. This data (Figure 9) from Susanne Hay and John Zupancic from Boston shows the cumulative number of babies and the number of trials from 1991 to 2016. You can see that the quantity of neonatal randomised trials has increased from <100 per year to just under 250 per year. I'm confident that the timeliness will follow, as will the quality and the size of trials.

"However, at two years of outcome, the total primary outcome of death, or MDI, in the population with 93% follow-up showed no difference...The German group had reported just a month before we did, and although a smaller study, had almost exactly the same findings. So I think we can be confident that transfusing infants to a high transfusion level within the ranges of the top algorithm does not confer benefits for death or long-term neurodevelopmental outcome."

Figure 9 Number of Trials and Infants



"This data from Susanne Hay and John Zupancic from Boston shows the cumulative number of babies and the number of trials from 1991 to 2016. You can see that the quantity of neonatal randomised trials has increased from <100 per year to just under 250 per year. I'm confident that the timeliness will follow, as will the quality and the size of trials."

In my final three slides, I must thank some people. First of all, I was privileged to be the student of some outstanding clinicians and scientists who helped me. In the UK, initially, there were Edmund Hey, Cyril Noble, and Malcolm Coulthard. In the Hospital for Sick Children in Toronto Paul Swyer, Karen Pape, and Mex Perlman. Then in McMaster Medical School Gordon Guyatt and Robin Roberts.

Throughout my Canadian and Philadelphia years, I was fortunate to have outstanding research fellows, including Tai Fai-Fok, John Zupancic, Mazen Al-Essa, Chad Anderson, Connie Williams, David Millar, Elaine Boyle, Sara De Mauro, Fliz Foglia, Eric Jensen, Maky Fraga, Ursula Guillen, Li Ma, Clyde Wright, and Nic Bamat.

I was fortunate to be in the Children's Hospital of Philadelphia (CHOP) for the last 15 years of my career.

I was very fortunate to have two outstanding division chiefs, first Phyllis Dennery, who brought me to CHOP. Then Eric Eichenwald was a second amazing division chief. I was very fortunate. Both Phyllis and Eric (were) incredibly supportive. The environment in which one is so important.

I must, of course, thank my wife, Barbara, together with whom I had a great many friends in academic life,

And I end by thanking the AAP and all of those people—the nurses, all at the bedside, the babies, and their parents, This is a painting by the German expressionist Otto Dix (that) displays one of these babies.

Thank you.

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