December 14, 2020

CONVERSATIONS WITH MIKE MILKEN

Sarah Murdoch, *Co-Chair, Murdoch Children's Research Institute (MCRI)*

Kathryn North, *Director, Murdoch Children's Research Institute (MCRI); David Danks Professor of Child Health Research, University of Melbourne*

Hamish Graham, *Paediatrician and Senior Research Fellow, Murdoch Children's Research Institute (MCRI); University of Melbourne; Royal Children's Hospital*

Mike Milken: One of the most dramatic things that's occurred over the last century has been the extension of life. In 1900, about half the people in the world died before their fifth birthday. Average life expectancy on the planet was 31 years of age. Today, it's around 73. And a great deal of that has been due to the advances in the treatment at childbirth, prenatal, and dealing with many life-threatening diseases that children face. And one of the organizations that's played one of the major roles has been the Murdoch Children's Research Institute in Melbourne. MCRI is not only the largest children's health research Institute in Australia, but it's ranked in the top three of institutions globally. You have 1,200 dedicated researchers and have a footprint in 35 countries.

We have the honor of having join us today Sarah Murdoch, Kathryn North and Hamish Graham. And Sarah, I'd like to start with you if we could. Give us a brief history of the MCRI, the population you serve, and what makes the MCRI so unique.

Sarah Murdoch: Thank you so much for this opportunity. I first just want to say that your commitment to education, to public health and to medical research over your lifetime has been really extraordinary. So we're really grateful to be included in this series of podcasts. MCRI was established by my grandmother-in-law, Dame Elizabeth Murdoch, who herself lived to 103. She established the Institute in 1986 and she did so because she'd been closely involved with the Royal Children's Hospital in Melbourne, Australia. And after seeing so many unwell children as she visited their bedsides, she said we must get to the root cause of these problems and prevent disease. So, she had the incredible foresight to establish MCRI. She focused on genetics, which is incredible in 1986, but of course she knew that we would face new problems in the future.

Over the 20-plus years that I've been involved, I've witnessed the transformation from Australia's top institute to now one of the world's top medical hubs, being co-located with the Royal Children's Hospital and the University of Melbourne's Department of Pediatrics, which has allowed for researchers and clinicians to work really closely together. As they do their promoting faster and more effective translational outcomes with much greater interaction with patients than is the case for most medical research institutes around the world.

So we're fortunate that we're located in Australia, as this is a place with a strong federal interest in genomics and in medical research. And we have a modern integrated public health system. With our footprint, as you said it's in over 35 countries, we have collaborations with other top institutes and universities around the world who are really looking to us for our data and for our expertise. So we really think of ourselves rather than a research organization powering for impact, we're really an impact organization powered by research.

> **"With COVID, there's been this renewed focus on the importance of medical research. My feeling is that with more funding and with philanthropic partners, I'm really, really optimistic about the further impact that we can make on that global scale."**
>
> **- Sarah Murdoch**

Sarah, there's so many organizations that wish they had an integrated effort of clinical, where they were actually treating patients, translational, moving from basic laboratories to the patient, and basic. Kathryn, let's talk a little bit about the team, how you recruit, how you retain, and some of the breakthroughs and leadership that the MCRI has had over the years.

Kathryn North: Our focus is always on how we can lead internationally, how we can contribute internationally. So all of our research programs across the Institute have international collaborations and international reach. We've now grown from initially a handful of researchers with a big focus on genetics to over 1,200 researchers and hundreds more students who are all really focused on how to tackle the big problems facing children. We've expanded our reach across genomics leading into stem-cell medicine. We really look at the modern epidemics that are facing children and adults through our links out into population and community health, and we really have a big focus on how we can make a difference. We always look at how we can retain and develop the very best people. We recruit both nationally and specifically very internationally as well. So, we have a very diverse team of people who have come from across the globe to work with us.

Let's talk about some of the organizations you've partnered with. I know the Gates [Foundation] and World Health Organization are two of the many, but let's talk about some of the areas that the MCRI has led the world in.

Kathryn North: We've been very involved in the global genomics effort and to be able to target what are relatively rare diseases. Although they affect around one in 20 children that are born, you need to really link globally to make things happen and to find diagnoses and treatments. We are one of the leading partners in the Global Alliance for Genomics and Health; I, myself, am the vice chair of that organization. It now incorporates over 500 institutions in over 100 countries. And it's backed by NIH, the Wellcome Trust, and our government has made a significant investment in genomics. Another big area has been in stem-cell medicine where we've really got some of the best researchers in the world that are able to harness the power of potent stem cells to differentiate our own cells.

So I could take your blood or your skin cells and transform them into kidneys that are composed of the same genetic makeup as you; of beating heart cells in a dish. And we're looking really at how we can apply that technology of developing a person's own tissues to actually treat disorders. For example, in congenital heart disease, how can we then create sheets of beating heart cells to mend those hearts? Kidney disease affects both children and adults with very high rates of kidney failure around the world. We're now able to grow mini-kidneys in the dish to look at how diseases develop and then do high through-put screening to look at the best treatments. And our eye is on the game of how we can actually develop kidneys themselves.

> "We've got our eye on the long-term impacts of COVID as well. We've had a 35% increase in presentations with mental health issues, just to our Children's Hospital. We've been looking at the impact on pregnancy and newborns, and we're also leading an international trial that's really looking at how we can protect health workers."
>
> - Kathryn North

We have also focused from the very beginning on how we can develop vaccines that are going to tackle major causes of death in low- and middle-income countries, so we have focuses on pneumonia, meningitis, gastroenteritis, and now obviously a big focus on COVID-19.

Well, you've made enormous progress in Victoria and Melbourne versus COVID 19. Can you share a little bit of what occurred over the last few months and what your experience has been recently?

Kathryn North: Within our country, at no other time in our history have the researchers been working in such partnership with government to influence policy and practice.

What we did was look across the Institute and mobilize all of our strengths that we could bring to get to bear to this huge issue. Within just a couple of weeks, a team of over 100 researchers were looking at how we understand the effects of COVID as an infection and the mechanisms by which it causes disease and really starting to screening drugs in terms of antivirals. But we've got our eye on the long-term impacts of COVID as well. We've had a 35% increase in presentations with mental health issues, just to our Children's Hospital. We've also worked with government to make sure our kids can return to school safely, and we now sort of have them in school and keeping them in school. We've been looking at the impact on pregnancy and newborns, and we're also leading an international trial that's really looking at how we can protect health workers from the perspective of COVID and their increased exposure.

> "Kidney disease affects both children and adults with very high rates of kidney failure around the world. We're now able to grow mini-kidneys in the dish to look at how diseases develop and then do high through-put screening to look at the best treatments. And our eye is on the game of how we can actually develop kidneys themselves."
>
> - Kathryn North

One of the things that you've just touched on was the collateral damage for other diseases. How have you been able to operate during this period of time with your researchers? How have you been able to maintain the level of research and care for the children?

Kathryn North: Within Australia, the medical research institutes are regarded as an essential service. So although we've really cut back, those who can work from home work from home. We've always had our laboratories operating and our research has really pivoted so that we do a lot of work remotely. Our stem-cell researchers, for example, have really focused on developing mini-organs from human stem cells of all the organs that are affected by COVID-19 and then working with engineers to build those organs, and then to test them with COVID infection and look at the mechanisms of damage, and then doing high through-put drug screening to work out how we can best treat that. And that is now gone from a local to a national to an international collaboration where we make all of that technology available very widely.

So our laboratory-based research hasn't slowed down at all. We do a huge amount of work across large birth cohorts that are now kids and adolescents, and some are multi-generational and how we keep an eye on those children and families. We've really utilized some unique strengths where we have quite a lot of previous data on the well-being, the health and the mental health of children and families in our community. But we've now been able to continue to liaise with those families, to look at the direct effects of COVID and then look out into future.

And finally, we were gearing up in April to launch one of the world's biggest birth cohorts, Gen V or Generation Victoria, which is enrolling over 160,000 infants born in Victoria over the next two years We've now built in a whole part of that, where we can focus on COVID. We've captured the pregnancies and bio-specimens of all the women who are pregnant across Victoria during this time, and now we're able to launch, as our COVID numbers have gone down, we're now able to follow that what is now really a COVID generation from their birth to look at all of the unexpected effects of COVID-19 and to follow them into the future.

The mental health area that you mentioned here is one that we've identified over the last 10 months of long lasting-effect on the family, losing a business, losing a job, not being employed, losing a loved one. But what about the mental health and the strain on your own researchers and workers at the MCRI?

Kathryn North: We've been so focused on that Mike over the last sort of six to nine months. And we've really made sure that we continue our outreach and our sense of community in the Institute, even though we've been in disparate locations. So what we've done is quite regular communications and outreach with our staff. And these are practices, I think, we'll take into the future as well; instead of having a big director's forum or town hall where you'd have hundreds crowding into a lecture theater, we're doing now by Zoom. And we get 700, 800 members of staff coming along. We tell stories about business-as-usual research, we talk about our own experiences and how we're feeling during the "Are You OK Week" I know that I could tell the story of how COVID has affected me and being removed from my family during difficult times.

And I think we've come out of this quite resilient. The feedback that we're getting is people still have felt connected. And I think the other thing is, not one person in the Institute lost their job due to what happened during COVID. We provided flexible working hours. We instituted Flexi75 so people received their full salary, but we told them we only expect you to be able to perform at 75% capacity. We supported parents who are homeschooling and looking after their kids. So I think the ultimate point of that is while we were trying to support resilience, we were also providing support for the people that were really feeling this the hardest. And we aim to do that on a very personal level.

I'd like to go to Hamish for a few minutes here, if I could. Hamish, you are a pediatrician with a particular focus on sub-Sahara Africa, Nigeria, Uganda; Uganda being one of the youngest countries in the world where more than half the population is under 16. How did you get an interest in this area?

Hamish Graham: Thanks, Mike. I think I got into medicine with this crazy belief that you've probably share as well, Mike, that people's health prospects shouldn't be determined by where they were born or the circumstances of their birth.

For me, it was probably about 15 years ago when I was working with medicines on the frontier in Sudan that I really saw the pointy end of this. And I remember my first week as a young doctor in the hospital there, I saw a young girl with pneumonia. She was very sick. She was breathing fast, breathing hard. She was semi-conscious. And you could see the fear in her parents' eyes. We admitted it at our hospital. We hooked her up to oxygen and gave her antibiotics. But we didn't have basic things like a pulse oximeter to check a blood oxygen level; we had only one oxygen concentrator, so if that was needed for someone else, she might have to come off it. And she did really well. But during my time there, I realized what it felt like to not have what you needed as a health worker to give even the most basic care like oxygen therapy to patients when they need it. And I guess that's what's driven me into it. I didn't imagine doing research, but you know, I love discovery. But perhaps the biggest priority is, how do you get these basic therapies like oxygen to the patients who actually need it?

"In some Nigerian hospitals over the last five years, we found that one-third of the children admitted with pneumonia needed oxygen. We found that about a quarter of the sick babies needed help breathing … Unfortunately it's common to see equipment graveyards in many hospitals, and that's really testament to a failing of the system."

- Hamish Graham

Let's talk about the challenges we have in the world, particularly in rural and emerging markets in the area of oxygen. What are the diseases that have at root a need for access to oxygen?

Hamish Graham: Great, great question. So we actually looked at this specifically in some Nigerian hospitals over the last five years, and we found that one-third of the children admitted with pneumonia needed oxygen. We found that about a quarter of the sick babies needed help breathing. But we also found that there were many other conditions – sepsis, malaria, meningitis – that in their severe form caused patients to have low blood oxygen level. We put some numbers together for UNICEF and some partners, and we found that 4.2 million children are admitted to hospital with severe pneumonia requiring oxygen therapy. Now that's just for pneumonia and those children have about a seven times higher risk of death. So it hugely increases your risk of death. But we also see that in the need for it in all the other conditions, including for adults, and I mean, COVID has been the obvious example of that, but it's not just COVID, it's many other conditions for adults as well. And that causes a lot of deaths. We can't put a hard number, but we're talking about hundreds of thousands, probably over a million preventable deaths each year because patients don't get oxygen when they need it.

Well, I know when I visit the wards for newborn babies, a number of them need oxygen. What are the things that bring that on?

Hamish Graham: In newborn babies, the three big killers are infection, sepsis, being born too early, prematurely, and both of those conditions are very closely associated with hypoxemia, low blood oxygen levels. And in places like sub-Saharan Africa, the third group is those with birth asphyxia, or complicated birth, so they haven't got enough oxygen as they start their entry into life. So those are the three big areas, and that's what strives at that number about a quarter of children needing help quarter severely of sick babies needing oxygen.

So I know you've developed a strategy here over the years to deal with this issue. Can you go over what is the potential solution?

Hamish Graham: I've got to say this has been a real collaborative effort. We've been working with governments, with local partners, and with NGOs, particularly recently with the Clinton Health Access Initiative, to make sure that every patient gets oxygen when they need it. Oxygen is not a new thing. It's been around for a long time and there's reasons why it's not accessible.

> "We've identified five countries – Nigeria, Ethiopia, Kenya, India and Uganda – five countries that together account for about one-third of this oxygen gap. We showed that the improvements in oxygen systems could make a big difference in terms of saving lives, reducing the risk of death from pneumonia on children in hospital by 50%; cutting it in half. That's very big."
>
> - Hamish Graham

There are four keys that we've identified and that we're trying to work around to make sure that oxygen gets flowing to the patients who need it. Firstly, we need to help healthcare workers identify who needs oxygen and to give it safely. And the key here is pulse oximetry, so using those small devices, probe on the finger to check blood oxygen levels. At the moment you'll rarely find a pulse oximeter used in sub-Saharan African hospitals outside of the operating theater. This is a big reason why only about one in five children who need oxygen are getting it. And yet we know that when we get pulse oximetry used routinely, it makes a huge difference to nurses and patients.

Secondly, we need to support biomedical engineers and technicians to get the right equipment and to repair and maintain it. At the moment, it's unfortunately common to see equipment graveyards in many hospitals, and that's really testament to a failing of the system to support biomedical engineers with the basics like spare parts, procurement and access to technical support.

The third thing is coordinated procurement at scale to really reduce the costs and make sure we're getting the right sort of equipment for the right context. And we've been

working particularly with Clinton Health Access Initiative, with administrators pooling procurement and reducing overall costs.

And the fourth thing is bringing this all together so that the decision-makers and funders have the right information to be able to make the important investment choices. We know that governments and hospitals are already spending a lot on oxygen and getting very little for what they're spending. So we believe, and we've shown this at sub-national scale, that if we tackle these four areas, we can make sure that the patients that need oxygen are getting it. And in many cases, we can actually reduce the costs, particularly in the long term.

> "We know that governments and hospitals are already spending a lot on oxygen and getting very little for what they're spending. We're talking about hundreds of thousands, probably over a million preventable deaths each year, because patients don't get oxygen when they need it."
>
> - Hamish Graham

When we think about medical research, medical care, there's kind of two forks here. One, can we deploy things we already know work and provide it to what are the largest populations on our planet that don't have access, and you've identified this four-point system. The second is, can we find solutions for diseases that there is no known solution in? One of the things that's so difficult for me and others to accept is the number of children that die due to the fact that we cannot provide them with what is low-tech, not high-tech, and the idea I think you've put forth here that in many cases there's equipment but it doesn't work when it's most needed. Now I know this effort, you've identified five countries to start with as the sample for the world. What are those five?

Hamish Graham: So this is a partnership between MCRI and the Clinton Health Access Initiative, CHAI. And we've identified five countries – Nigeria, Ethiopia, Kenya, India and Uganda – five countries that together account for about one-third of this oxygen gap, this lost opportunity, and countries that we've already got established relationships with governments and local partners. And I'm really excited about this because I don't see it ending there. We've already been working with a number of these countries. We've got foundations around policies and strategy. But I think what we can learn and what we can prove in these countries will hopefully have effects even beyond. We've got another 10 countries that we would really like to be able to be doing this work in, but these five countries, we see as the big opportunity countries to build something that will change the systems, not just there, but hopefully across sub-Saharan Africa and Asia.

Take us back to, what is life like in a rural medical facility? You know, many of us have never been there. I visited a few, but if I'm bringing my child in, what are the challenges they have?

Hamish Graham: I think a lot of the emphasis in hospitals has been on the big end of hospitals and we've seen this particularly with COVID. But it's really the smaller hospitals, particularly the rural, remote hospitals that both admit the most sick patients, but also have the most opportunities for building capacity. We've been working in hospitals in Nigeria, in Papua New Guinea; each hospital's very different, but you can imagine in some of these more rural, remote hospitals, you might have just one doctor or maybe even not even staffed by doctors. It's a long way for patients to travel to get care, even coming to the hospital, and if they need a higher level of care, then even further for them to go and that costs money and effort and takes people away from their families.

It can be a lot of pressure for the healthcare workers working in that sort of situation. I just reflect on some of the feedback that we've got from our work in Nigeria. We showed that the improvements in oxygen systems could make a big difference in terms of saving lives, reducing the risk of death from pneumonia on children in hospital by 50%; cutting it in half. That's very big.

> **"We've expanded our reach across genomics leading into stem-cell medicine. We really look at the modern epidemics that are facing children and adults through our links out into population and community health, and we really have a big focus on how we can make a difference."**
>
> **- Kathryn North**

But probably what sticks with me even more is what I hear from the families and the healthcare workers when I visit. I remember visiting one hospital on my most recent trip and a mother clearly wanted to talk to me and we sat down together and she told me how scared she'd been when she first brought her child. She was worried that there wouldn't be any care available, that there wouldn't be anything that they'd be able to do for her child, and she was worried that she wouldn't be able to pay for it. Now her child had pneumonia, and oxygen was a big part of that treatment. For her to be able to see that the healthcare worker was able to test her blood oxygen level, give her oxygen, and it wasn't going to use up all her savings - it's going to give her back a precious baby alive that she could take home clearly meant so much to her. And as the nurses around me reflected on this, they said, it's that sort of story, which motivates them. For them, oxygen had been a real headache, a real something that they just felt was that almost futile. They knew patients would need it, but they just didn't have the capacity to give it. And what had changed for them was they were now able to provide a level of care that was much better, this basic level of care, but it made a big difference to the health care workers and to the patients that they were treating.

So technology and the potential role it might play, the ability to charge where there's no power system. What role have the developments in solar played in the ability to deliver oxygen today or in the future?

Hamish Graham: That's a really exciting thing, and it's something that we explored both in Nigeria and also in the remote highlands of Papua New Guinea. Some of these hospitals had no reliable power at all or it was cutting out multiple times a day and you maybe you wouldn't have power throughout the night. So for us, we were largely using oxygen concentrators, which are small sort of bedside machines, but they require they require power 24/7. So being able to use existing solar technology, to be able to make sure that those concentrators could run 24/7 regardless of what else was happening, made an enormous difference. And I think that we also saw differences with reliable power far beyond just running an oxygen concentrator. It meant you had lights overnight when mothers were giving birth. It meant that staff could walk around the facility at night without it being dark, tripping over steps, and knocking equipment over; like very practical things. So I think that's a really exciting area that we'll see a lot more in, as particularly solar technology becomes more and more affordable.

Well, one, we couldn't be more excited about the field you've picked, and we couldn't be more excited about this initiative, Hamish, that you are part of and the potential to save the lives of millions of children a year with the technology that's already available to us by making it available to them.

Kathryn, 35 countries you deal with – how do you relate with the people inside the MCRI with these partnerships and efforts and things like Hamish is focused on? How do you bring that back to Melbourne?

Kathryn North: It's really a two-way street. This immense global reach that we have with the Institute. We send our people out to work on the ground, but most importantly, we're working with the local governments and training up the local people so that they are able to deliver at the bedside and to their communities directly. And we also bring people from the countries we work with on exchanges back into Melbourne and provide them with scholarships and fellowships so that they're doing free training with us.

And just for an example, we have quite a significant outpost and a lot of work in Fiji. We've bought in trainees from Fiji who've done fellowships in the neonatal intensive care who have gone back to really set up and build that expertise locally. We went to visit one of these in neonatal intensive cares in Fiji, and the death rate in that nursery had decreased by 50% over the preceding three years due to that expertise and being able to provide what really we see as essential care. We are a global institute, everything we do, we look at how it can translate much more broadly than just our shores.

Well, thank you, Katherine. Sarah, I'd like to come back to you if I could. Obviously, just being associated with this Institute is uplifting. And the reason that I visited is it's made

has an impact globally. How can people help you? What does the MCRI I need to keep this momentum and progress going?

Sarah Murdoch: Thank you, Mike. It's wonderful that you made this such a huge effort to come see us. One of the things you told us is that we mustn't see ourselves for where we are located geographically. And I think that's really right. You can see that the impact we are having globally, and that's from basic science. So, now how do we keep this momentum going? Well, you know, we haven't historically enjoyed the levels of funding that the U.S. institutes receive yet. We're really at the same level and really competitive in our impact. It is through philanthropy that we've been able to see really some incredible research. Some of the research we're doing right now on a BCG [Bacillus Calmette-Guérin] vaccine for frontline healthcare work started out with small funding and ended up with a fantastic investment by the Gates Foundation. With COVID, there's been this renewed focus on the importance of medical research. My feeling is that with more funding and with philanthropic partners, I'm really, really optimistic about the further impact that we can make on that global scale. There's so much more to be done as you say, so we really just appreciate so much Mike highlighting our work, highlighting the work of the Institute, and in particular highlighting Hamish's work. I mean, it is critical, and we really hope he has all the very best success because I really do feel he's going to make an extraordinary difference to the lives of so many children.

> "Our footprint is in over 35 countries. We have collaborations with other top institutes and universities around the world who are looking to us for our data and our expertise. We think of ourselves as an impact organization powered by research."
>
> - Sarah Murdoch

Many people have found that in terms of investment return on their philanthropy, being able to do something in the emerging markets or sub-Saharan Africa, South Asia particularly, that you can deploy existing technologies to millions of lives and improve the quality of life. Whereas a lot of the other work that we've really focused on has been to try to find solutions for diseases where there is no solution. When you see children dying, not because we needed a new therapy or a new vaccine, but we just didn't deploy what we know works, it really breaks your heart. So, we thank you for your leadership. We thank Kathryn, Hamish for joining us today; we wish you the best and enormous success on your efforts in the future.

Sarah Murdoch: Thank you so much.