Diana Bianchi, M.D.

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Barr: Good afternoon. Today is January 4th, 2023. My name is Gabrielle Barr, and I'm the Archivist at the Office of NIH History and Stetten Museum. Today, I have the pleasure of speaking with Dr. Diana Bianchi. Dr. Bianchi is a Senior Investigator with the Center for Precision Health Research and the head of the Prenatal Genomics and Therapy Section for the Medical Genetics Branch at NHGRI [National Human Genome Research Institute]. She's also the Director of NICHD [Eunice Kennedy Shriver National Institute of Child Health and Human Development]. She's going to be speaking about some of her experiences and research leading up to her time at NIH. Thank you very much for being with me.

Bianchi: My pleasure, Gabrielle.

Barr: To begin, will you please share a little bit about your upbringing in New York City, such as your early family life, education—including your years at the prestigious Hunter College High School—and any formative experiences you had that you feel really shaped you as an adult today?

Bianchi: Well, thank you, Gabrielle, for that question. I was born in New York City but spent the early part of my childhood in Westchester County. I mention that because I have a distinct memory of baby rabbits being born in our backyard as well as seeing my cat give birth to kittens under my bed. That is really an important formative experience, because I think that left a big impression on me—watching the whole process of the cat giving birth, and then also drying off the kittens, which is what got me into trouble with my mother.

Barr: How old were you when you witnessed a cat giving birth to kittens?

Bianchi: I was probably three or four. I can remember the membranes, I remember the blood, and I remember the kittens coming out—so it was a big impression. Nobody in my immediate family is in medicine, although both of my parents worked during my childhood. My parents got divorced when I was nine years old. That's why we moved back to New York City. I'm a first generation American. My mother was born in Berlin and emigrated because her background is Jewish—was Jewish; she's no longer alive. My father was Italian, and they met in South Africa. I'm very proud of the fact that I'm a first generation American. I was very influenced by my maternal grandparents who had escaped Hitler and were very proud to be American, and I think that's going to be important when we connect the dots to giving back to America because I feel very strongly about that. We didn't have a lot of money when I was growing up. I was very fortunate to be accepted into Hunter College High School, which was from seventh grade onwards through twelfth grade. Although it is no longer only female, at the time it was. A few years behind me was Associate Justice Elena Kagan. Since it's become co-ed, there are a number of other famous alumni such as Lin-Manuel Miranda and Chris Hayes, if you're a fan of MSNBC. It’s a terrific place that does not charge tuition. It was highly diverse even then. I appreciate that even more so because this past June I attended my 50th high school reunion and reconnected with the women in my class—I mean, I just was amazed at how accomplished my classmates were and what a diverse and rich environment it was.

Barr: What was it like for you to go to an all-female school, and what effect do you think that had on you?

Bianchi: Well, that's a great question. I think it was very important in the sense that we were never treated as second class citizens. We were given a full complement of science courses, and I think that was extremely important. We were not distracted by dating or other such activities. There was no internet back then, so we were in a fairly protected environment within the larger environment of New York City, which of course had a lot of cultural activities. But it was an opportunity to focus on scholarship and develop deep friendships with other young women. The other thing that's very important for the later picture is that we were required to do a senior thesis. Through a family friend, I obtained an internship in the cytogenetics lab at Roosevelt Hospital in Manhattan. As I remember, I spent a significant part of my senior year in high school working there.

Barr: Were you always interested in science and medicine? You said you were fascinated with animals and your cat, but when did your "structured" interest in science and medicine begin and how?

Bianchi: Well, I won the sixth-grade science fair, so I think that by that point I had already developed an interest. Hunter had a very strong science program. They had Advanced Placement (AP) science courses, so I was able to build upon that interest. I was somewhat of a mutation in my family. My mother was an actress, and my father had a Ph.D. in economics, but when he came to the United States, he worked in the hospitality business. He was a country club manager for most of my childhood. I was very different from them.

Barr: What was it like working in the cytogenetics lab?

Bianchi: There were several things that were interesting about it. First of all, it was the first time I had worked in a hospital. It was the first time I had worked in a laboratory. At that point chromosomes could be visualized under the microscope, but they were stained in a very homogenous way. It was before the banding technique was developed, which was in 1974. Now you know how old I am. This was in 1971 and 1972. You could identify the chromosomes by their size and by the position of the centromere. You couldn't really determine if there had been rearrangements within the chromosomes, but you could determine if something was missing, or if a chromosome had broken apart. My job was to investigate if blood samples from women who were heroin addicts had damage to their chromosomes. That was a research question that was being asked by the lab. In addition, I was exposed to a number of pediatricians, both men and women, which was very important. That's when I began to think about how it might be interesting to go to medical school and become a doctor.

Barr: What encouraged you to attend University of Pennsylvania as an undergraduate, and will you speak a little bit about your time in college?

Bianchi: The University of Pennsylvania has its medical school right on the undergraduate campus. That was important for me. It was also a pioneer in terms of having a separate Department of Human Genetics. This was as early as 1972 and 1973. There were very few schools that had a separate Department of Human Genetics at that time. The fact that you could live in the college dormitories and work in a research laboratory was very attractive to me. Plus, it was in a city, Philadelphia. I was used to living in Manhattan. It was not far from home, but it was far enough from home. It was also a very exciting time because Philadelphia was getting ready for the United States bicentennial in 1976, so there was a lot going on culturally. But I think the most important thing for me was the ability to have the

exposure to the medical school, the hospital, to go on genetics rounds, and again, to meet more female professionals. At that time, it was hard to find role models, but I had role models who were clinical geneticists—physicians practicing genetics—and also post-doctoral fellows and Ph.D. geneticists who were women, who had families, and who were very inspirational. That all tied together to make Penn attractive as a school. Because of my experience in my senior year of high school, it was very easy for me to walk into a laboratory in the Department of Human Genetics and say, “I know how to do a human karyotype. How can I help?” They assigned me a project that was similar to the first project I had worked on, where there was a concern about women who used spray adhesives in advertising. Now everything's done on a computer, but in those days when marketing posters were made, they were using a type of spray glue and that was supposed to damage chromosomes. I did a fairly large study looking at chromosomes and looked at breaks and gaps. I’d have to go back and look at that publication. That was my first publication. I'm going to have to check this, but my memory is that it did not show a dramatic difference between people who had been exposed and people who hadn't been exposed. But I did get my first publication.

Barr: That's exciting. Did you work in other labs as well when you were at the University of Pennsylvania?

Bianchi: In the summer, to earn money, I worked in the clinical cytogenetics lab. When people went on vacation, I helped out, because, again, I knew how to perform a karyotype. When patient samples came in from children who had various medical problems, then I would either help to culture the cells, help set up the slides, or look at the material under the microscope. It would still be cross-checked by a faculty or staff member. Then in my senior year, I worked on another project looking at tumor cell lines from neuroblastoma, looking at chromosome rearrangements there. I had a number of experiments.

Barr: You had such a variety of experiences. Will you discuss your experience as a medical student at Stanford University, including how you connected with Leonard Herzenberg, who was studying the use of flow cytometry to develop a non-invasive genetic screening or diagnostic test for Down syndrome, and what skills you feel like you learned from him and others that have shaped your career?

Bianchi: Well, yes, it did. Professor Herzenberg presented me with a research problem that I've effectively followed for many decades, and it has spun off into several areas, some of which we are pursuing today at the NIH. I went to Stanford because I needed a change from Philadelphia. As a native New Yorker, I always had a fascination with California and what was going on in California and why everybody wanted to move to California. The Stanford curriculum was very research intensive. Instead of having classes five days a week, they had classes three days a week, and then they encouraged you to do research on Tuesdays and Thursdays. I don't know if it's like that now, but it was like that then. Again, I parlayed my experience from Penn into a genetics experience at Stanford. I first met with Dr. Howard Cann, who is no longer alive but was a pediatric geneticist. I told him what my experience was and that I wanted to get involved in research, and he said, “You need to speak with Leonard Herzenberg.” I went to meet with Leonard Herzenberg, who is also unfortunately deceased, but his wife, Lee Herzenberg, is alive, and they were co-investigators in their laboratory.

Their lived experience was that they had a son, Michael, who had Down syndrome. I believe he's still alive. This story is told on that NPR broadcast “Only Human.” Lee Herzenberg was pregnant in approximately 1959, so this is before or around the time that it was recognized that Down syndrome was caused by an extra copy of chromosome 21. There was no prenatal diagnosis or prenatal testing at the time, and the biggest risk factor was for a woman of advanced maternal age, meaning over 35. She

was not over 35 at that time, so there was no reason to suspect that the pregnancy was at risk for any abnormalities. The way they told it to me was that initially when Michael was born, they didn't realize he had Down syndrome because there was no chromosome test to confirm it. It was confirmed several years later. I believe at the time they confirmed it by radiographic studies in which they measured a pelvic angle. The Herzenbergs were surprised by Michael's diagnosis. They thought there really needed to be a way that a couple would be told ahead of time that there's a suspicion that the baby will have Down syndrome, to enable them to educate themselves or to have a choice about continuing the pregnancy. When I walked into the lab, they said, "We want you to develop a noninvasive prenatal diagnostic test for Down syndrome." There had been a postdoctoral fellow in the lab there before me. He was returning to Finland. They said, "Well, we want you to start working on this. We have developed the fluorescence activated cell sorter and we want you to figure out a way to isolate intact fetal cells from the blood of a pregnant woman using monoclonal antibodies. Then, under the microscope, we want you to confirm that these are fetal cells."

At the time, the only way that you could do this was to show that the cells contained a Y chromosome from a boy baby—to show that it's not the mother's cells. You would have to take couples where, for some antigens, the mother didn't have it and the father did have it. We used monoclonal antibodies against one of the HLA antigens, which are antigens on the surface of cells that are inherited and that relate to your own immunology. As a medical student, I had already learned how to draw blood. They would send me all over the bay area to draw blood from a pregnant woman and her partner, and then we would figure out which couples had the right combination of an HLA A2 negative mother and HLA A2 positive father. Then we would use antibodies against HLA A2 positive cells, figuring that those cells, if present in the mother's blood would be cells from the fetus. Then we would look under the microscope to see if those cells had a Y chromosome. We were looking at cells that were in interphase, so they were non-dividing cells. By this point—this was 1974, 1975—we could use a green, fluorescent probe mapped to the Y chromosome that would mark a male cell. We did that and came out with highly significant results indicating that there were fetal cells circulating in the blood of a pregnant woman (1). The problem is they weren't there in a high enough number, although subsequently, NICHD funded a major study called the Non-Invasive FeTal cell study (NIFTY), in which we tried to isolate the cells and use them for clinical diagnostic purposes. We showed that there were never enough to use for clinical diagnosis. That hasn't stopped other investigators from trying, even today, but we were successful in the sense that we could show that these cells were circulating in the blood of a pregnant woman (2). The key was to find antibodies against cells that would be more universal, because in this first proof of principle study we could only show that it worked in the right combination of couples. We needed something that would universally mark fetal cells or embryonic cells. In the context of doing that, we were exploring multiple different antibodies and came up with a combination that marked stem cells, and that's when we realized that, actually, cells would circulate from prior pregnancies as well as the current pregnancy.

Barr: Wow. For how long do the prior pregnancy cells circulate?

Bianchi: In our studies we demonstrated that they were circulating for decades (3). A woman who's been pregnant is carrying cells from every one of her fetuses, so that was pretty dramatic when we recognized it. We replicated that information in mouse models as well, using mice that carried certain genes that would make their cells fluorescent so we could track where the fetal cells go in the pregnant dam or the mouse mother. They go predominantly to the lung, but they also go to the spleen, the liver, and to other organs. That really revised our concept of how a person changes after having a baby. The pregnant person carries cells from her various pregnancies, and some of these cells have the capacity to repair damage to the mother's organs, which is amazing.

Barr: Is it the same number of cells for every single pregnancy or do more recent pregnancies have more cells?

Bianchi: That's a great question. We were never able to really study that. We wanted to see if there was a favorite child, so to speak. Was there a child that, for whatever reason, was able to colonize the mother more so than another child? We don't know that. And the other thing that's important is, although we could only prove that the cells were fetal when they were male at the time, the so-called microchimerism, where the fetal cells get into the mother, is the same for male and female cells. We were later able to show that with unique HLA genes inherited from the father.

Barr: What about mothers that have multiple pregnancies, but also some of their pregnancies are of multiple babies? Has that been looked into?

Bianchi: We didn't study that. Again, because there are two babies, there are two placentas, there's a lot more blood flowing back and forth—you would think you would have more. And that may be why we had a very easy time detecting the cells in mice. In general, the mice that we were working with had 6 to 8 pups per pregnancy. The bottom line is you are always in your mother, and the mother then sends cells back to the fetus as well. Now we know—we didn't know at the time, but now we know—the mother's cells are really important for educating the fetus's immune system, so it's actually a two-way transfer. But the volume of cells from the fetus to the mother is more than from the mother to the fetus. Dr. Judith Hall wrote a commentary about one of our scientific papers and she wrote, "Your mother's not only looking over your shoulder, she's <u>in</u> your shoulder."

Barr: Very interesting. Will you briefly talk about your residency at Boston Children's Hospital, as well as your fellowship at Harvard—places that you later ended up working at as a neonatologist and geneticist—and were there particular reasons why you chose to train at these institutions?

Bianchi: Thank you for those questions. The big issue here was what specialty to go into. It's going to be important when we get to why I was interested in the position as Director of NICHD. I could not decide whether I wanted to be an obstetrician or a pediatrician. I love both specialties. I loved the babies, and I was fascinated in genetics because of the transfer of DNA from parents to child. It's all connected. I ended up at Boston Children's because by that point I was missing the East Coast a little bit. Also, at the time, Stanford had a very small pediatric hospital. It doesn't anymore, but there was a relatively low birth rate in the area. It seemed like the East Coast hospitals had bigger patient volumes, a lot more acuity, and more variety in terms of pediatric diseases. I spent some of my summers as a child in New Hampshire, and I always liked New England. That, in combination with the fact that Boston Children's was a very research-intensive hospital with a highly ranked residency; it was my first choice. Pediatric residency lasts for three years. In my senior year at Stanford, I did a sub-internship in neonatology. That's how neonatology comes in. Again, that was during the time when I was trying to decide between pediatrics and obstetrics. I found that I was always much more interested in the babies than the mothers in terms of long-term follow-up. That's ultimately how I made the decision. Plus, obstetrics and gynecology were largely surgical specialties, whereas pediatrics is more of a medical specialty. That's why I ended up on the baby's side. But I got to neonatology because of my sub-internship in my fourth year at Stanford Hospital. I was just fascinated because these babies, who are largely premature, are truly making the transition between life in the womb to life outside of the womb. There are so many things that the neonatologists have to do to recreate what would be normal physiology while still *in utero*. I just thought that these babies were amazing with what they could actually do. These tiny, tiny

babies all had personalities. The thought of truly helping these very immature, premature babies and helping them to live a productive and long life to me seemed very fulfilling at the time. That's how I got to neonatology.

It was natural after the residency in pediatrics to think about a subspecialty. I was recruited early on in my residency to join the neonatology-perinatology program at Harvard, which was called the Joint Program in Neonatology, because it was three different hospitals within the Harvard system. It's interesting, genetics was not yet a recognized specialty at the time, but I was always interested in genetics because of my background in cytogenetics. I was also very interested in human development and syndromes and how you identify syndromes on the basis of a child's appearance. I recognize now—I didn't recognize then—that I'm a very visually oriented person. Pattern recognition is very important in medical genetics, and I'm able to do that and find that interesting. The same thing is true looking at chromosomes. Once you memorize what normal chromosomes should look like, then you can do it manually. Now computers do it, but at the time it was important to do it manually. I had informal training in genetics because it didn't exist as a specialty, but as it became a specialty, I think around 1982 or so, I did what was required to become board certified in genetics. I've always seen a connection between the two, but it's only fairly recently that the field seemed to be merging even more because now in neonatal intensive care units around the country, genome sequencing is being offered to babies that don't have a diagnosis. I always saw them as connected, as well as prenatal diagnosis and prenatal genetics and genomics being connected, but it's really over time that the connections have become more obvious to the rest of the world.

Barr: You joined Tufts in 1993, teaching in the medical school as well as founding and heading the Mother Infant Research Institute. Will you describe what was involved in getting this institute off the ground, and did you draw inspiration from other programs or centers, either nationally or internationally?

Bianchi: Okay, so there's a long period of time between joining Tufts and founding the Mother Infant Research Institute, or MIRI, as we called it. I went to Tufts in 1993 because of my multidisciplinary interests. Again, I couldn't decide between obstetrics and pediatrics, and in fact saw them as connected. Some of my favorite teaching conferences at Boston Children's were the prenatal diagnosis conferences, particularly when they were talking about prenatal ultrasound findings—at that time, prenatal ultrasound was just getting off the ground as well. I was at Boston Children's, where life begins at birth, and most adults over 18 would go to Brigham and Women's Hospital, which was connected to Boston Children's Hospital by a bridge. But there was very little interaction between the faculties of Brigham and Women's and Boston Children's, even though they were both Harvard teaching hospitals.

I was recruited to Tufts, and it was very attractive because they were much more oriented in a multidisciplinary fashion. By going there, I could interact much more easily with the maternal fetal medicine specialists. I was recruited to start a program in reproductive genetics and to do prenatal genetic counseling and supervise the genetic counselors. I was also expected to work as a neonatologist, which allowed me to see the babies that were born after I had counseled the parents, and then start a research laboratory. I got a very generous package which made it very attractive. That was a big reason why I went to Tufts. It just seemed like the faculties were much more collaborative and, in fact, I made very close friendships and relationships with the head of maternal fetal medicine, Dr. Mary D'Alton, and the then head of pediatric surgery, Dr. Tim Crombleholme. The three of us co-wrote a textbook called "Fetology: Diagnosis and Management of the Fetal Patient," which was an attempt to provide parents and health care providers with information about a prenatally diagnosed condition from the perspective

of what it means for the mother and what it means for the baby. Does the baby need surgery? What does it mean for the baby's medical care? And what's the long-term prognosis, as well as the genetic risk for having this occur again? To me, that crystallized the very best of Tufts because we were able to write the textbook together, contributing our perspectives.

Barr: Did you have to take a lot of medical ethics at this time because all those questions kind of bring those issues out in society?

Bianchi: Well, I've always been interested in ethics, and in fact, I'm now collaborating with the Department of Bioethics at the Clinical Center. Yes. A lot of these cases do raise ethical issues. I took required ethics courses, but it was more that there was discussion of ethics with regard to some of these cases. How far should we go? What is the prognosis? There were definitely ethical questions raised about some patients. I remember one in particular, interestingly, who had Down syndrome and had a congenital heart defect. At the time I was the neonatologist who made the decision that the baby should go on ECMO—extracorporeal membrane oxygenation—while we were trying to figure out whether this heart defect was something that would be viable long term. I remember the case because there was a big discussion. Should I have done that? Was this right to offer this really extreme type of therapy to a baby with Down syndrome? I felt that we repair hearts all the time for babies with Down syndrome who have congenital heart defects. This was just another version of that. Ultimately everybody agreed that that was the right thing to do. I also remember another case, that was ultimately published, where I went to the delivery room, and it was a family who had a prior history of a baby who died due to homozygous alpha-thalassemia, which is a type of hemoglobin that's incompatible with life. This baby was born. There had been no prenatal testing. The baby was perfectly formed, was having a little trouble breathing, and was pale. We resuscitated her and as part of that, gave her a transfusion. Well, it turned out she had homozygous alpha-thalassemia, so the question was, should we have done that? By giving her the transfusion, we essentially gave her life, but we were also committing her to a lifetime of transfusions because her own hemoglobin does not support the transfer of oxygen to tissues, so she's transfusion dependent. On the other hand, at that point, once she had gotten the transfusion, she was no different from some of the other hemoglobin disorders that require transfusion. We published that case. Interestingly, sometime in the last five or six years, this person, who is now an adult was presented as a hematology case discussion at Beth Israel Hospital, and I got to meet her virtually! I felt good because she told us that she doesn't have any regrets about her life, although she did talk about her rebellious teenage years. She's a delightful person who, essentially, other than being transfusion dependent and having to deal with iron overload, basically lives a normal life. Those are two of the more dramatic cases that posed ethical questions that I remember.

Barr: We'll talk more about some of your research. Will you comment on your efforts to develop noninvasive ways to conduct prenatal testing, such as through, at first, cfRNA [cell-free ribonucleic acid] and then later cfDNA [cell-free deoxyribonucleic acid]? What were some of the challenges you encountered and where do you see this discipline heading?

Bianchi: I've mentioned to you about trying to isolate intact fetal cells from maternal blood. There were never enough present to be able to reliably predict which babies were going to have a chromosome abnormality. It was in 1997 that Dennis Lo, from the Chinese University of Hong Kong, but who was then in the U.K., made the observation that you could find cell-free DNA from a fetus in the blood of a pregnant person— so maybe you didn't need to look at intact fetal cells, maybe you needed to work with only DNA. He first proved that you could do that by looking for Y chromosomal DNA in the blood of a person carrying a fetus. We collaborated with Dennis and did some of our own research that

suggested that there was even more cell-free fetal DNA present in the blood of a person carrying a fetus with Down syndrome. We gradually recognized that the DNA was coming from the placenta, not predominantly from the fetus. It was also a marker of placental well-being. But what really made the difference, in terms of the leap to actual clinical implementation, was the development of massively parallel sequencing techniques—and also the fact that after a certain point in the 2000s the equipment that you needed to do this became affordable for an individual laboratory. Dennis Lo at the Chinese University of Hong Kong and Stephen Quake at Stanford—whom I never met at Stanford because he wasn't there at the time—both recognized that you could use the massively parallel sequencing technique to determine ratios. You could map fragments of DNA to certain chromosomes and then determine ratios, for example, of chromosome 21 to another chromosome. If the fetus had three copies of chromosome 21, you would detect an excess amount of chromosome 21. That would suggest that the fetus had trisomy 21. Those observations were really unique, and we were very intrigued.

At that point, I started a collaboration with Verinata, the company which ultimately became acquired by Illumina, to do clinical trials to really scale this up, because the original cell-free DNA studies had only been done on small numbers of participants. We were able to show that this technique of massively parallel sequencing was much more effective in terms of identifying which fetuses had chromosome abnormalities—initially trisomy 21, then trisomy 18, then trisomy 13, and then abnormalities of the sex chromosomes (Turner syndrome or Klinefelter syndrome, etc.) (4). The massively parallel sequencing techniques became widely available in about 2008. By 2010, we were doing clinical studies to compare fetal aneuploidy screening using cell-free DNA with biochemical and ultrasound markers, which were the standard of care. By 2011, the technique became clinically available to patients. It has revolutionized prenatal screening, for better or for worse. It is much more accurate than the other methods that are used, which include biochemical measurements as well as certain ultrasound measurements of the back of the fetal neck, for example. Those so-called standards of care have about a 5% positive predictive value, which means that there's a 95% false positive rate. When you do cell-free DNA sequencing, the positive predictive value is generally over 90%, so it's 5% versus 90%. Cell-free DNA sequencing is much more accurate as a screen for fetal aneuploidies, and that's why it's been incorporated into clinical care in less than a decade. It's totally changed the way prenatal screening is done for the major chromosome abnormalities. For example, the state of California has now gone to a protocol where this is the standard of care. It's the first-tier testing, as it is in several European countries. In a decade, it's gone from laboratory to widespread implementation. It's had a major impact. Then there have been a number of other areas that we've researched. For example, rare autosomal trisomies. This technique can pick up atypical findings in any of the chromosomes. What we've found is that abnormalities in certain chromosomes will result in the fetus being small for its age or other abnormalities, such as predisposition to miscarriage when there are three copies of chromosome 16 or three copies of chromosome 15. Currently at the NIH, we are doing a study to look at how the routine prenatal genetic screening can detect cancers that are occurring in the mother. I'll talk about that probably in the second part.

Barr: There's been some research about using prenatal genetic screening for some psychiatric conditions. It's not as developed as some of the other ones that are looked at, but can you comment on that?

Bianchi: Not really. For example, for autism there are so many genes that are involved. People talk about the potential of prenatal screening for autism, but it is nowhere near as developed as the whole chromosome abnormalities or even some of the microdeletion syndromes. You also asked about cell-free RNA, which is very interesting because prenatal screening is currently focused on chromosome

abnormalities, but in fact they are relatively rare. If you think about all of the complications of pregnancy, the so-called great obstetrical syndromes are preterm births and preeclampsia, in which the mother develops life-threatening hypertension, kidney failure, and liver failure. There's great interest in trying to identify which pregnant people are at risk for either having a baby prematurely or developing a severe complication of preeclampsia. Back in the 2000s, we looked at particular biomarkers, genes that the fetus was expressing near the time of a full-term delivery. There were clear genes that indicated to us that there was some sort of developmental clock going on (5). The fetus was getting ready to be born. That work has been built upon now by other investigators who are showing specific genes that are upregulated when these pregnancy complications are about to occur. There's nothing that's in widespread use as of this moment with regard to cell-free RNA, but it is probably one of the most active areas of ongoing research at the present time.

Barr: How have advances in fetal diagnostics influenced fetal treatment?

Bianchi: That's a great question too. I think the ability to see the fetus in a clearer and clearer way has enabled us to recognize that there's a lot of atypical development that's occurring prenatally. Certainly, in my laboratory, we've been very interested in treating neurocognition in Down syndrome—but you could say this is true for any condition in which the developmental profiles are starting to go awry. If you could treat prenatally, presumably by the time the baby's born, you would have minimized the pathology or at least have begun a treatment regimen. It's a combination of better visualization of the fetus through more sophisticated imaging, but it's also a recognition of what the fetus is doing biochemically, and it's also the ability to do genomic sequencing or really understand genetic disorders and where you might have the ability to treat. I had mentioned alpha thalassemia before. There's now a big trial going on at the University of California San Francisco to treat alpha thalassemia prenatally.

Barr: Can you comment further on your work in isolating intact fetal cells from maternal blood as a noninvasive way to obtain fetal material for a genetic diagnosis, and how that led to the whole field of fetal cell microchimerism?

Bianchi: The hope with intact fetal cells is that if you have a cell that you know is fetal, you don't have to differentiate it or differentiate the DNA from the maternal DNA. That's the problem with using cell-free DNA or cell-free RNA. It's a mixture of the maternal blood. That's why the ratios are used, because if the mother has typical chromosomes or is euploid, there wouldn't be excess or deficiency of one of the chromosomes. If the fetus has an extra chromosome, you can pick that up amidst the mother's chromosomes. But if you're working with intact fetal cells, you don't have to worry about that because you just have the fetal material right there. The difficulty, as I said, is the limited amount of material and the ability to recognize a uniquely fetal cell. I mentioned that we had been looking at stem cells, but the mother has stem cells, too. To my knowledge, there's never been a perfect fetal antibody that recognizes only fetal cells. You would always still get some combination of fetal and maternal cells. But when we were looking at the stem cells, that's when we recognized there were cells that were remaining in the circulation from a prior pregnancy. Microchimerism refers to the fact that there are two populations of cells. There's the majority population, which is the mother's own cells, and there's a micro or minority population that is coming from fetus or fetuses.

Barr: Can you speak a little bit about your work in founding and heading the Mother Infant Research Institute [MIRI]?

Bianchi: If we want to [speak] chronologically, at Tufts, I started out to build a prenatal genetic and genomics clinic and eventually became the vice chair of the Department of Pediatrics at the Floating Hospital for Children, which was the Tufts Pediatric Hospital.

Barr: What were some of your responsibilities in that regard?

Bianchi: A lot of it was mentoring pediatric investigators. It was also advocating for funding, putting together teams, and helping the trainees get the experiences that they needed. It was mainly thinking about the best ways to organize the various research programs, making sure that they had the facilities, the equipment, and the personnel that they needed, and trying to encourage collaborations with other departments.

Barr: A lot of what you do now.

Bianchi: Well, yeah, it is related. The Floating Hospital for Children was originally a boat; that's where the "Floating Hospital" name came from. Then it came on land in the 1930s. After I came to NIH, it became known as Tufts Children's Hospital, but unfortunately, it no longer exists. It was closed in the summer of 2022, which was very difficult. That was, I guess, a financial decision because of the need for more adult beds due to COVID. But let's go back a few years and progress up through the ranks. I came to a certain point in 2008 where I felt that I needed a change, and I also felt that I needed leadership training and counseling about what options were available. I applied for the Executive Leadership in Academic Medicine program that is run by Drexel—also an all-female program, interestingly. There were a lot of similarities with Hunter, but it was like a grown-up Hunter High School experience. The point of that program was that women were accepted from all over the country with mainly M.Ds., some Ph.Ds., some public health specialists, and I think a few dentists as well. It was intensive training about academic health centers in all aspects—financial, leadership, etc. I went to that program during 2008-2009, in addition to working full time. We had to have an action plan as part of our graduation requirements. We had to develop something. I was very interested in the fact that there were three other research institutes at Tufts Medical Center, but nothing devoted to either pregnant people or children. It was one of the strengths of Tufts Medical Center. It still is because they kept their neonatal intensive care unit. They've got a very strong maternal fetal medicine program. There are very few research institutes in North America that are examining some of the common problems—let's just take prematurity—from both the maternal perspective as well as the pediatric perspective. My vision was to put teams of multidisciplinary investigators together to commonly approach a particular scientific problem.

As part of my action plan, I received counseling and support to develop this program and make a business case for it. I did that as part of the graduation requirement, but then I brought it back to Tufts and said, "I think we really need this, and here's why, and here's the business plan." And they agreed. There had been three other research institutes—there was a medical oncology research institute, a molecular cardiology research institute, and more of a public health institute, but nothing building on the strengths of the Floating Hospital, as well as the obstetric unit. That became MIRI, the Mother Infant Research Institute. We started with six investigators, half of whom came from obstetrics and half of whom came from pediatrics. And it's still there today, I'm happy to say. They're actually doing quite well. Tufts Medical School and Tufts Medical Center's research programs, which were separate when I was there, are now in the process of merging, and I have been told that maternal child health, as represented by MIRI, is going to be one of the pillars of the combined research programs. I'm very, very happy about that.

Barr: Definitely. During your time at Tufts, you also engaged in a lot of other initiatives. You were an editor for several scientific publications, you served on some different boards, and you were also a part NICHD's advisory council. Can you speak a little bit about how these different experiences shaped your scientific thought or have helped you get a better grasp of the field at large?

Bianchi: Sure. I served on several editorial boards, but I was also Editor-in-Chief of the journal Prenatal Diagnosis. There's another connection to prenatal screening and diagnosis. I served as the Editor-in-Chief from 2007 until 2020—13 years. It was a great opportunity to see how a field evolved, to really be on top of all the cutting-edge research in this relatively narrow area of medicine. Also, I enjoy editing. I relished putting together special topic issues, so that was really a great experience. I also served on a number of professional society boards, which was terrific experience in terms of networking. In 2012, I was invited to serve on the NICHD Advisory Council, which was of great interest because the majority of my research funding came from NICHD. It was an opportunity to see how the secondary reviews were done, how funding decisions were made, where the institute was going, and the problems that they dealt with. I served on the Advisory Council for just under four years, and I remember being sad at my last meeting when they asked for exit comments, having absolutely no idea that I would become the next permanent Director of NICHD.

Barr: Is there anything else that you'd like to share about your trajectory before coming to NIH?

Bianchi: The thing that strikes me now is that mentorship and junior faculty startup packages—there's a lot more effort now on enabling junior faculty to succeed. Don't get me wrong, I'm not bitter about this in any way, but the culture at the time that I was coming up through the academic system was basically sink or swim. There were a lot of fish that got thrown into the sea, and only the strong would survive. At the time we were very accepting of what we were given. It's much different now. Junior faculty are much more empowered. They ask for more. They're given more. There's much more of a focus on helping people succeed then there was back then. To tell you the truth, there were also differences between what male colleagues were given as opposed to female colleagues. There's much more of a recognition of that now.

Barr: Did you see that among your colleagues firsthand?

Bianchi: Oh, absolutely, yes. There are pictures of me on the internet with a broom where I'm sweeping the floor in my very first laboratory because it was in rough shape when I was handed the key. I was thrilled, however, to have my own laboratory and to have my first grant funded, which resulted in the ability to hire a technician. I was not given a technician as part of my initial package.

Barr: Did you encounter a lot of overt discrimination because you were a woman?

Bianchi: I wouldn't say it was overt. It was probably more subtle. There are a couple of other anecdotes that I do want to share that I think are important to the overall story. One of my very first grant applications when I got to Boston Children's when I was a fellow was to the Joseph P. Kennedy Foundation, and it had to do with something related to isolating fetal cells from maternal blood. That grant was not funded, and I was very disappointed. For some reason, I kept the letter, and the letter was signed by none other than Eunice Kennedy Shriver, who founded NICHD and for whom the institute is named. I will sometime show that in a talk to say that you just never know in what direction your life is going to turn. I remember being very upset that this first grant application wasn't funded, and if

somebody had said, “Just wait, you are going to direct the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development,” that would have blown my mind at the time. That's the first anecdote.

The second is, you can't see it, but in my office, I have a handwritten letter from Jerome Lejeune. I had no memory of writing this letter, but apparently, I wrote him a letter in 1973 or 1974 when I was at the University of Pennsylvania, asking to work in his laboratory. Now, why did I ask him specifically? Professor Lejeune was credited as being the first person to recognize that people with Down syndrome had three copies of chromosome 21. I had the experience in cytogenetics. His laboratory was in Paris. That certainly played a role in my asking to work in his lab, but I wanted to learn more about chromosomes in people who had developmental disorders. He wrote a lovely handwritten letter back in French. Apparently, from what he says, I wrote to him in French. And he, in a very charming way, is saying, “I'm sorry, but I don't have space in my laboratory right now. Can you wait until autumn of 1974?”—which I couldn't do because of my pre-med requirements. I had forgotten I had written that. It kind of comes full circle because I was interested in Down syndrome then, but then I must have forgotten about it until I met the Herzenbergs and they said, “We want you to develop a noninvasive prenatal diagnostic test for Down syndrome.” There are these two letters. People don't really write letters anymore, but apparently, I saved the important letters, and I probably should frame the one from Eunice Kennedy Shriver and put it next to the one from Professor Lejeune. But I think sometimes there are these little hints of what's to come, and unless you save your letters, you probably won't recognize them.

Barr: Well, thank you. I look forward to our next session when we’ll talk about your NIH experiences.

SECOND INTERVIEW

Barr: Good afternoon. Today is August 18th, 2023. My name is Gabrielle Barr, and I'm the Archivist at the Office of NIH History and Stetten Museum. I am back with Dr. Diana Bianchi. Dr. Bianchi is the Director of the National Institute of Child Health and Human Development. Today she will be speaking about NICHD’s efforts towards mitigating the COVID-19 pandemic. Thank you very much for being with me.

Bianchi: Thank you, Gabrielle. It's good to see you again. It’s been a few months since we last spoke.

Barr: Definitely. A lot’s going on! Will you discuss the input of the trans-NIH Working Group on Pregnant and Lactating Women and Children that NICHD co-leads and the research priorities in the implementation of the study?

Bianchi: Sure. I think that's a really important thing to discuss, because it was essential in getting the NIH studies on COVID that affected children off the ground. One of the things that most people don't realize is that we are the National Institute of Child Health and Human Development, and many people both within and outside of NICHD, think that we cover all research related to children, and that is not true. Pediatric research is supported by every NIH Institute and Center, with the exception of, say, the National Library of Medicine and a few others. But the ones that are doing biomedical research all support child health research. Realizing that, in 2018 we formed the NIH-wide Pediatric Research Consortium to encourage all of the groups that were doing pediatric research to harmonize their efforts and to collaborate so that we could speak with a bigger voice. If you took all of the pediatric research

across NIH, it's around $4 billion. That's quite a lot of support. This group has been regularly meeting every other month since 2018.

When the pandemic began, the consortium, which we call N-PeRC [NIH Pediatric Research Consortium]—an acronym for this pediatric research consortium— quickly formed a subgroup to focus on how the pandemic was affecting children. This was very prescient and, in a way, almost revolutionary, because if you remember at the beginning of the pandemic, the focus was on the elderly and the immunocompromised. Everybody thought at that time that children didn't get sick with COVID. By working together and serving as persistent advocates to include children in NIH's major COVID-19 research programs—such as Radx, the Rapid Acceleration of Diagnostics, or the RECOVER [Researching COVID to Enhance Recovery] programs—and by advocating for inclusion of children, this working group was able to facilitate more than $5 million in supplemental funding for research projects early in the pandemic in fiscal years 2020 and 2021, so that we could start addressing issues in children. The RADx-Radical [RADx-rad] program, which was technology-based, included the Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence Study, which was led by Dr. Bill Kapogiannis. It's a mouthful, but we call it the PreVAIL Kids Study. The goal of the PreVAIL Kids Study was to develop innovative point of care approaches to understand the factors that influence the range of symptoms present in children infected with SARS-CoV-2—and importantly, to distinguish SARS-CoV-2 infection in children from other inflammatory diseases like Kawasaki disease or children with fevers who were presenting to emergency rooms. The PREVAIL Kids study had eight different groups who ended up working together but were looking at different aspects of SARS-CoV-2 infection to provide rapid diagnostics. And some of those studies are now transitioning to commercial applications, which is a great success.

Barr: While you're talking about RADx, can you talk about some of the other ways that NICHD has been involved with this program, such as supporting children going back to school, making sure that tests are child friendly so that children of a certain age can administer tests themselves, and a whole other range of things?

Bianchi: It took a while for it to become recognized that children were being profoundly affected by the pandemic. They were not in school. They were isolated from their friends. They had a major shift in their daily lives. At first it wasn't recognized as the serious mental health toll that children experienced during the pandemic—and continue to experience. Never mind the educational effects of the pandemic—being out of school, and then the disparities in terms of access to a laptop or access to Wi-Fi. Could they actually participate in online education? The focus in the beginning was on life and death issues and not so much on children. We recognized that children had important issues of their own, but they also had to get back to school so their parents could get back to work. The children were in the middle of this economic puzzle. We began to advocate for getting children back to school and, in fact, started what was initially called the Return to School program, but later called the Safe in School Program. It was a fairly large program that was administered by the Radx-UP Underserved Populations Study. The lead at NICHD was Dr. Sonia Lee. We funded programs all over the country that included diverse populations such as American Indians and also, importantly, children with intellectual disabilities. Some of the mitigation efforts like wearing a mask or washing your hands, are much more difficult to administer in children who have intellectual disabilities and don't understand why you have to wear a mask or why you have to wash your hands.

You asked about children administering their own tests. One of my favorite studies in the Radx-UP program was in the Return to School program—a group of middle school students who were in an

underserved community in St. Louis who became the researchers themselves. They did a study in their own school as to whether their classmates preferred taking oral tests, in which they would spit into a tube, or if they preffered the nasal swabs. I saw their presentation and their result was that their colleagues or their friends preferred the nasal swabs, because they said it was faster and they weren't prevented from eating or chewing gum. They became engaged participants, which was just another kind of cool secondary effect of the studies.

We were able to show a number of things. For example, studies that we supported via the Pediatric Trials Network showed that mandatory masking in schools reduced cases of COVID-19 during the surge associated with the Delta variant. The Return to School and Safe in School program was not exclusively focused on children. It was also focused on teachers and support staff. It was really very broad looking at the entire school community, and it was very well received in the communities that we funded.

Barr: You also brought up RECOVER. Can you discuss how NICHD has contributed to RECOVER, especially the experience of looking at MIS-C [Multisystem Inflammatory Syndrome in Children], which is a really strange phenomena that several children have experienced following their recovery from COVID-19, and which connects with the Caring for Children with COVID program?

Bianchi: Let's talk first about MIS-C, because MIS-C was a new disease, and it kind of came out of nowhere a few months after the initial variant. What happened was that children in England and Italy were being hospitalized with serious life-threatening illness, where they had low blood pressure, severe respiratory illness, were critically ill, and had inflammatory conditions of the heart. They were in intensive care units and children died, but most of them actually recovered with intensive care support. But in the beginning, nobody knew what was happening. That's really the arrival of MIS-C, this new inflammatory condition, which in many ways resembled an existing well-known condition called Kawasaki disease. That's what brought the world's attention to the fact that children could get sick and could get critically ill. I often tell a story that I received a call on Mother's Day of 2020 from Dr. Collins. He said, “What's going on with MIS-C and what can we do to address this new condition in children?” We initially joined with NHLBI [National Heart, Lung, and Blood Institute] and NIAID [National Institute of Allergy and Infectious Diseases] to combine protocols that we were all doing individually to study MIS-C in children. Our contribution to that was to use, again, one of our existing clinical trial networks, the Pediatric Trials Network, to gather data from dozens of sites. That network has about 100 hospital sites in it, and they're studying medications given to children. That network pivoted to studying drugs that were already being given to adults with COVID. This was a way of helping to understand the safety and efficacy of different drugs in treating COVID in children. I already mentioned PreVAIL Kids, which had eight different programs. They formed a mini network. They didn't know each other before the start of the PreVAIL Kids study, but they all collaborated and then they applied for funding as part of the RECOVER program. Again, in the beginning it wasn't clear if children would have so-called long COVID. They do, and they are very much included in the overall RECOVER program. There are over 10,000 children right now that have already been enrolled in that. Their manifestations of long COVID are somewhat different than adults. It's very interesting that symptoms have been reported in athletes who've been exceptionally healthy but suffer from cardiac inflammation after the infection. Now, most of the kids with long COVID did not have MIS-C, so they are somewhat separate, and the cases of MIS-C are definitely decreasing substantially. MIS-C seemed to be more commonly associated with the Alpha variant and the Delta variants, not so much with the current Omicron variants that are circulating now.

Barr: Do you think that the increased rate of children being vaccinated has had any effect on rates of MIS-C?

Bianchi: Sure. I mean, the overall numbers of infections have gone down. Children have been vaccinated. Or children have been exposed and have developed immunity to COVID without necessarily being vaccinated but being exposed to it in the community. That is probably part of why there are fewer cases now.

Barr: Can you speak a little bit about how NICHD has leveraged its Best Pharmaceutical for Children Act [BPCA] program in evaluating treatments for those younger than 18, especially as children are excluded from some of the early trials for COVID therapeutics?

Bianchi: The Best Pharmaceuticals for Children Act, or BPCA, authorizes research to improve the safety and efficacy of medication used for children. The goal of the Act is to improve safety and efficacy of drug use and dosage for children by providing rigorous clinical data to approve drug label instructions. I'm a former neonatologist. We would give many drugs off-label to neonates—so the drugs are approved by the FDA for adults and then they are used off-label. There's a tremendous need to know more about drugs that are being used routinely in children. Like I said before, the Pediatric Trials Network [PTN], which is charged to implement the BPCA, has more than 100 clinical sites, both outpatient and inpatient. And again, you will hear the recurring theme throughout our discussions today that we made use of existing networks. That's one of our major lessons learned—that it's so important to have an existing infrastructure to be able to respond immediately or within a few months. The PTN has been in existence for many years, and we thought it would be important, as I said, to study the drugs that were already being given to children who were hospitalized with COVID, to be able to learn more about their safety and efficacy. It's not that we were conducting a clinical trial in the classical sense—we weren't giving the drug to compare it to a placebo. What we were doing is studying children who were given these drugs as part of their treatment. It's an opportunistic study. There were six drugs that were being tested, including remdesivir, which was being used as a treatment for COVID in adults.

Barr: Another population that NICHD covers are pregnant people and mothers. Would you discuss how you have worked with the NICHD-funded Maternal-Fetal Medicine Units Network (MFMU), which includes the GRAVID [Gestational Research Assessments for COVID-19] study, to launch a national study of 24,500 pregnant women, and some of the things that have been learned from all these studies?

Bianchi: That's a great segue from your previous question because, like I said, as soon as the pandemic began, we started looking at understanding how the infection is going to affect our populations. NICHD's populations include children, people of reproductive age, pregnant people, and people with intellectual and physical disabilities. We were already thinking about how, even though those populations were not the focus in general, we had to be ready. We've had the Maternal-Fetal Medicine Units' Network, or MFMU, in existence, and we've supported it, since the mid-1980s. There are 12 academic medical centers in the United States, and they cover more than 160,000 deliveries each year. When the pandemic started, the network began to think about how the virus would affect pregnant people because, again, nobody was even thinking about pregnant people. "Talk to your doctor." That was the advice. The doctors didn't know anything because there was no evidence for pregnant people. The MFMU investigators got together and thought about how they could use the massive new infrastructure here to do the GRAVID study. GRAVID is not a separate network. GRAVID was a study using the MFMU Network. GRAVID is an acronym for Gestational Research Assessments for COVID-19. The question was how is COVID-19 going to affect pregnant people? We didn't really know at the time if there would be increased morbidity and mortality. How would women who get infected during their pregnancies compare to pregnant women who did not get infected, and what would be the outcomes for both the

mothers and the children? This study was published and included 24,500 participants. Very importantly, results suggested that cases of severe COVID-19, but not mild COVID-19, were associated with a higher risk of having a cesarean section delivery, higher chance of bleeding postpartum right after delivery, higher chance of having a preterm baby, and other complications, such as stillbirths. These results were added to evidence that the CDC had to develop guidelines for pregnant people and, importantly, for the physicians and other care providers treating pregnant people, to inform them about risk and decision-making during pregnancy.

This led directly to the question about vaccination because nothing was said in the initial guidelines regarding vaccination about pregnant women. All that was said was “talk with your doctor.” That was basically the initial advice, and it was very frustrating for many care providers because they didn't know if the vaccine was going to be safe in pregnant people or not. Actually, the CDC started a registry that was very helpful and asked for voluntary registration if a pregnant person had had the vaccine, whether they had any complications or not. That was the initial evidence that we had, but then subsequently, we supported a study to better understand whether the virus was going to be transmitted from the mother to the baby, and also whether it was going to appear in the placenta. Many viral infections show damage in the placenta. One of the intriguing things about SARS-CoV-2 was that it wasn't obvious whether the virus was damaging the placenta. We needed to do a study to see what the effects of vaccination during pregnancy were. We showed very conclusively that vaccination during the pregnancy improved the mother's health. In other words, the severe complications that we had seen in the beginning from people getting sick during pregnancy were mitigated by vaccination. But also, the antibodies that the mothers made following vaccination crossed the placenta and got into the baby and protected the baby for the first six months of life. That was even more dramatic when it came to breastfeeding studies. Some of the antibodies that the mother made following vaccination passed into the breastmilk. When people asked me the best way to protect their baby, the answer was to get vaccinated in the third trimester and then breastfeed your baby, and that is going to keep your baby safe. The vaccine at that point was not being studied in very young children. Vaccination in children came after some of our studies looking at vaccination in pregnant people. It took quite a while—months to years—to have the studies done in children, and they went from the older children to the younger children. The youngest babies were the last to be studied. In the meantime, we were recommending that pregnant people get vaccinated in the third trimester and breastfeed to keep their babies safe.

Barr: Can you also speak about the studies NICHD conducted and supported that looked at the effect of therapeutics like remdesivir in pregnant and breastfeeding women?

Bianchi: This gets at an area that's somewhat of a sore spot at NICHD. I've already implied that pregnant and lactating people are often excluded from research. One of our other big initiatives is PRGLAC [The Task Force on Research Specific to Pregnant Women and Lactating Women], something that came out of the 21st Century Cures Act which has to do with research on pregnant and lactating women and encouraging more research on drugs being given to pregnant and lactating women. We thought broadly about this because it's not only drugs, but it’s also devices like vaccines. We felt like this is something that we had to understand more. We had to understand about how drugs like remdesivir were going to affect pregnant people. Again, we used another existing network. In this case, it was one of our HIV networks. This is something that's supported not just by NICHD, but by NIAID and NIMH [National Institute of Mental Health]. In this case, we used the IMPAACT Network, which is the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, to study the effects of remdesivir in pregnant people who were already being prescribed the drug to treat COVID-19. That study was done at 17 sites in the continental United States and Puerto Rico. The data from that study resulted in the FDA

approving a supplemental new drug application for remdesivir, and the product label has been updated to note that the clinical trial data has not identified a drug associated risk of adverse maternal or fetal outcomes if remdesivir is being used in the second and third trimesters. Here's where our NIH research was used to change care and to give the information that the care providers needed and otherwise didn't get.

Barr: Definitely. Another population area that you support are those of reproductive age. This was a major topic in society. Can you discuss how NICHD has supported research that looked at how both the vaccine and the disease affect fertility and menstrual cycles?

Bianchi: Yeah, so this is a great question and it's shocking how little research is done on the menstrual cycle. This is an area of focus for NICHD. During the pandemic and once the vaccine became available, we asked NIAID, “Are you doing anything in this area? We're getting a lot of inquiries.” And they said, “No, no, you can handle this.” We were interested because soon after the vaccine became available, in early 2021, there were reports on social media of the menstrual cycle changing dramatically as a result of vaccination. That led to more social media reports that suggested that vaccination would seriously reduce fertility or make people infertile. Now, we didn't think that would be the case, but we needed data. Whenever you don't have data, all kinds of theories can circulate. We were able to provide supplemental funding to researchers already being funded by NICHD who were studying different factors that affect the menstrual cycle. We had a number of researchers who were using, for example, apps on the phone and how people were using the apps and how they were tracking their menstrual cycles. I forget exactly how many people we funded. It was probably like five or six where they got supplemental funding to see how vaccination affected the regularity of the menstrual cycle. Because we were able to use existing research groups, it's amazing—within a year of getting funding, we already had study conclusions and publications that showed that vaccination resulted in a temporary increase in the length between cycles immediately after vaccine administration. That difference only lasted one or maybe two cycles. After that, everything went back to its regular interval. Subsequent studies by the researchers showed that the length of time that a particular person was bleeding did not increase. There was no increase in pain, and it didn't make people irregular. It just slightly increased, by 1 to 2 days, the length of time between menstrual cycles. It was really interesting. We had an enormous amount of interest from the media—from social media, yes, but the traditional media as well. I remember doing many interviews at the time, and I think to date, the number of hits on the press release and media articles was record breaking for NICHD. There was a true gap for information and there was genuine interest in what we found. We're hopeful that that information was helpful to people to reassure them that vaccination would not affect their menstrual cycle. Then the second question came up, “Well, does it affect your fertility or not?” We did an additional study that showed that vaccination did not affect overall chances of conceiving a child, and this held true if either or both partners were vaccinated. The study, however, did reveal a temporary decrease in male fertility in the two months following infection, not vaccination. There was no effect of vaccination on subsequent fertility, which is interesting.

Barr: That is really interesting. It’s nice to see the numbers.

Bianchi: Yes!

Barr: Will you highlight some of the basic science research that NICHD has been engaged in, both intramurally and extramurally, such as investigating how the virus works, how type 5 inhibitors can prevent SARS-CoV-2 infections, the infectivity rate of certain variants and why, the effects of certain therapeutics like TEMPOL, and many others?

Bianchi: Yes. We have a fairly large intramural research program. I think people outside NIH don't necessarily realize that we have a campus. There are around 20,000 people working on themain campus in Bethesda. NIH has the largest research hospital in the world in the middle of the campus. Of course, with the biggest public health problem in our lifetimes, everybody wanted to do something. Everybody was thinking about how we can pivot our research efforts to address this major problem. We didn't really talk yet about how the pandemic affected our intramural program, but it did, because initially there was a lot of concern about being at the bench—being in a room with other people not knowing what the ventilation parameters were like. Laboratories were shut down for a period of time during the initial stages of the pandemic, and in fact, our program was one of the first that had an infected person working on site. I remember the weekend of March 15th in 2020, when it was becoming clear that we had a really serious problem. At that point we had our first person who was symptomatic with COVID-19 and there was an enormous amount of fear. People were exposed to the person; the person had handled a lot of common equipment. We had to shut down a whole building to be decontaminated at the very beginning. We had to tell people they could not come in to work. The Clinical Center, the research hospital, shut down as well. There were no outpatient studies being conducted and only interventional studies for critically ill people were being performed, but everything was being done with a reduced staff. Trainees were told to work from home and there was a profound effect on them as well. That was in the initial stages of the pandemic.

I think people used their time at home to reflect upon how their individual research efforts can help anyone and everyone. We were just really pleased with how our intramural staff thought about the pandemic and thought about their existing research. Many of the projects found potential pathways for the virus to infect cells, as well as understanding why the Delta variant was more transmissible than other variants. The Delta variant was much more significant for pregnant people. Dr. Tracy Rouault, whose work involves iron sulfur clusters, thought that the experimental drug TEMPOL that you mentioned could be used as a possible oral antiviral treatment. In her laboratory, studies in human cells showed that TEMPOL could limit SARS-CoV-2 infection by impairing the activity of a viral enzyme called RNA replicase. They have shown that TEMPOL prevents viral replication and reduces disease severity, but that's in hamsters. [laughs] Now they are transitioning to studying TEMPOL in human patients with early COVID-19, but the results are not yet available. There are many other examples. For example, in our former Detroit Perinatal Research Branch, they were doing a lot of work looking at the placenta and what the receptors are that are being used to either block the virus or transmit the virus to the fetus. The bottom line is that our intramural researchers were very committed to using some of their resources and building upon their existing research to help understand and treat the pandemic in different ways.

Barr: Can you comment on some of the psychological and developmental studies related to COVID-19 at NICHD—either conducted intramurally or supported—such as COVID's effect on learning loss in those with dyslexia, its effects on substance abuse amongst Native American adolescents, and child psychosocial development post-COVID? There were many others, so you're welcome to bring up whatever resonates most with you.

Bianchi: Yeah, I previously mentioned the profound educational effects. We have within our extramural branch a Child Development and Behavior Branch led by Dr. Jim Griffin. This branch has always studied typical child development, in particular how the children acquire language, for example, and various research projects associated with learning and school. They have baseline data against which to compare the effects of COVID-19 and the increased use of digital media and this transition to online

learning on the mental health of children. I mean, you and I are speaking by Zoom today. It's normal now. We've adapted to that, but for children, it's a very different experience. I previously mentioned the potential for educational disparities resulting from social disparities. This is a major long-term problem, and I think it's going to be one of our biggest issues following the pandemic. For some of the mental health issues, we are collaborating with the National Institute of Mental Health to study are how the isolation during the pandemic, this increased transition to online communication. All of that is under study now. I don't have any specific results to share with you. You asked about Native American adolescents. Native Americans are included in all of our large-scale studies that have been supported by RADx-UP, RADx-rad, and RADx Tech.

Barr: They were hit so hard by the pandemic, especially in the beginning. Are there certain aspects of COVID-19 research that you would like to study further, especially as the pandemic transitions to a different phase?

Bianchi: Yes, definitely. This has been a global experience. I talk with colleagues around the world and there's really been no equivalent in our lifetime, where everyone was working from home, and everyone was concerned about safety. We still are very concerned about the long-term effects of COVID-19 on pregnancy. We're very concerned that five years from now we're going to see a spike in mental health disorders, or even later on that we'll see an increase in cases of schizophrenia, which have been associated with viral infections. It's really still too early to tell. The first of the babies born during the pandemic are 3 to 4 years old now. We've had one NICHD study that has already been published that suggested that for children who were born during the pandemic, it didn't matter whether their mothers had COVID-19 or not, that they were slightly delayed from a neurodevelopmental perspective at six months of age. Now, why is that? Is it related to just overall stress? Is it related to isolation? Is there something else going on? But it is a real finding. We have that, living in a pandemic world, in addition to the possible effects of being infected. The effects on early childhood education are profound and need to be understood better—is it more math than reading, is it more reading than math? Also, the mental health effects of isolation, and, again, this increased use of digital media and the disease mechanisms. What's unique about this virus? It does not seem to affect the placenta in the same way, as I mentioned before, that other viruses do. Part of it has to do with the receptors on the virus. But very, very importantly, we need to be prepared for the next pandemic, which everybody says is not an “if”, it's a “when.” We're trying to take the lessons learned and be prepared.

Barr: Will you speak a little bit about that? As institute Director, what was your role in ensuring everyone was safe, redirection of funds, bringing staff back to campus, and maintaining morale? There's a lot of things that you do aside from just overseeing the science. What do you feel that you and NICHD have learned relating to the pandemic—both successes and failures—and how will that steer future research?

Bianchi: Those are great questions. I already mentioned that weekend in mid-March. It reminded me of my old on-call days as a pediatric resident. We literally pulled an all-nighter to try to figure out what to do because there was no NIH-wide information available at the time. We were the first or second Institute that had an infected person who had been all over Building 29. We had to make decisions on the fly. Our focus immediately was on the NICHD family—keeping the staff safe, recognizing the extreme anxiety of not knowing what was going on, not knowing if we were going to die, not knowing who we had been exposed to. This was truly, truly, truly a team effort. I cannot say enough of my leadership team at the time. For example, we had an Acting Scientific Director running the intramural program. At first it was Dr. Mary Dasso and then later on it was Dr. Chris McBain. Both had so much dedication to

initially providing guidelines and then doing walk arounds to make sure that people were adhering to the guidelines. Rodney Rivera, who's our Executive Officer, did an amazing job in terms of overseeing all of our safety efforts and then working with IT to get our extramural staff equipped with laptops so they could work from home. That's one of our big successes—that people got the equipment they needed so they could continue to do their jobs. Dr. Alison Cernich, who is our Deputy Director, was always on the front lines holding together all of these efforts and keeping us in touch with what was happening, for example, at the Health and Human Services level. Dr. Rohan Hazra, who's the head of the Division of Extramural Research, was working with his staff—who largely were working from home—to make sure that they were doing their jobs, and they had the support that they needed. Dr. Cernich worked extensively to start a series of monthly—well, they were more frequent in the beginning—town hall meetings, to provide a way of communicating with our staff and letting them know what was happening, because nobody was on campus. They proved to be very effective in terms of communicating information that was vital for everyone to know. They were so successful that we've continued them to this day. They're now on a quarterly basis and not exclusively on COVID. But the town halls really held everybody together. I'd like to think that they were helpful for morale, and they always included a wellness section. We talked about immediate things—what you can and cannot do, the science that we're doing, where we have learned things. But then we would always have a section on your own personal wellness. We were very concerned about that and recognized the toll that the pandemic was taking on everyone, and especially on people with families, who not only had to do their jobs, but they also had to supervise children who were at home. Again, this whole experience was really unprecedented for everyone who is living nowadays. The previous major pandemic was in 1918. None of us were around in those days.

Barr: In addition to COVID-19, NICHD has had to address other health crises such as maternal mortality, as well as the opioid crisis that continues, unfortunately. Can you comment on those two things?

Bianchi: Yes. The opioid crisis was present before the pandemic, but the pandemic has exacerbated it. Going back as far as 2017, more or less, when I started at NIH, we recognized that children, and specifically infants, who experience neonatal opioid withdrawal syndrome because their mothers have misused opioids was a big problem. We formed the ACT NOW Network, which is Advancing Clinical Trials in Neonatal Opioid Withdrawal to address how best to treat infants who are undergoing withdrawal. One of the things that we did—here's the theme again, using existing infrastructure—is to have a Neonatal Research Network. Then there is the ECHO [Environmental Influences on Child Health Outcomes] program that is supporting the IDeA [Institutional Development Award program] States Pediatric Clinical Trials Network. The Neonatal Research Network, like the Maternal-Fetal Medicine Units Network, has been in existence since the mid-1980s. It's very mature. These investigators had a lot of experience, but they were located in sites where there wasn't a huge impact of neonatal opioid withdrawal. In contrast, in the ECHO program, those sites are in rural areas with high incidence of neonatal opioid withdrawal, but with less experienced investigators. They partnered to form ACT NOW. The first thing they did was to show that no hospital around the country, no neonatal unit around the country, was using the same approach to treat infants withdrawing from maternal opioids. Knowing that was the case, they started to design studies that would provide evidence to give a standardized approach. The first one of these was the Eat, Sleep, and Console Study, which was just completed recently and published in the New England Journal of Medicine in May. Basically, what that approach does is that it evaluates infants for withdrawing for their ability to eat, to sleep, and to be consoled. The problem with babies who are withdrawing is that they're very irritable, jumpy, and they typically cannot be consoled when you touch them. What's been used in the past, when I was practicing neonatology, was something called the Finnegan Neonatal Abstinence Scoring Tool, which looks at 21 different

symptoms. It takes a long time for the nursing staff to evaluate a baby, and the baby gets a score. If the score is above a certain number, then they get medicated with opioids or phenobarbital or something else to calm them down. Nobody wants to give medicine to a baby who doesn't really need it. This eat, sleep, and console approach was first reported in 2014, but it had never been studied in a rigorous way. This study looked at each individual nursery using their previous way of treatment, and compared it to eat, sleep, and console (E, S, C). Each individual nursery was a site, and at the end of the day, they had well over a thousand babies that were in the study. It showed that the eat, sleep, and console approach reduced medical readiness for discharge by a week, and also significantly reduced the percent of babies that ever needed any opioid medication to control their withdrawal. It's much kinder, it's easier for the staff to administer, and importantly, it includes education of the family. It includes incorporation of the family in the treatment of the baby. It promotes breastfeeding. There were a lot of other aspects to it that really bode well for the long-term bonding and treatment of the baby. The babies in the study were followed up to age three months, and there were no adverse effects of of the E, S, C approach. That was one of the things they were concerned about and were studying—if undertreating babies with medication would have any adverse effects. And the answer was no. There's a longer-term study of these infants that's going on for two years to see their outcomes. Again, it's a problem that has gotten worse with the pandemic, but we are very happy that we had a very clear outcome with the Eat, Sleep, and Console Study and we're hoping that it will ultimately change practice.

Maternal mortality also got worse with the pandemic. It's a serious problem to begin with in the United States—with the health care resources that we have, we should not have the level of mortality and severe morbidity that we already have. Right before the pandemic in December of 2019, Dr. Collins, Dr. Perez-Stable, Dr. Gibbons, and I all went to a meeting with the Black Maternal Health Caucus, and we were essentially shamed by Congress, who asked us to do more to address the problem of maternal mortality. In the next few months, right around the time the pandemic was starting, we created an NIH-wide initiative that's known as IMPROVE—Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone—to reduce maternal mortality and reduce maternal morbidity. Now, I'm speaking like it sounds like it's just one thing, but it's actually a very, very complicated problem to solve. We have this phrase at NIH called “tin cupping.” For the first two years of the program, we went around with our tin cup to all the Institutes and Centers and to the Office of the Director saying, “We need to do something. Please consider giving us some money so that we can provide supplemental funding to researchers to address the problems.” We strategically decided to address the biggest problems that result in maternal mortality—for example, postpartum hemorrhage, postpartum cardiovascular disease, cardiomyopathy—that postpartum women experience. That is the leading cause for Black women to die from in the year following delivery infection.

Once the pandemic started, we included studies of COVID-19. The CDC has very impressive data showing the increase in the rise of maternal mortality, presumably due to COVID-19 infections. We also included maternal health issues and postpartum depression. For the first two years, fiscal year 2020 and 2021, we were able to provide supplemental funding. In fiscal year 2022, Congress recognized the IMPROVE Initiative and gave us a separate appropriation, and that led to a much more formal approach to the governance. I co-chair this initiative with Dr. Shannon Zenk, who's the director of the National Institute of Nursing Research (NINR), and Dr. Janine Clayton, who is the Director of the Office of Research on Women's Health. It is an NIH-wide initiative. We have an executive committee with representation from multiple Institutes and Centers, as well as a task force. You mentioned at the very beginning of our discussion that you saw the press release on the Centers of Excellence, which is the core activity of fiscal year 2023. We are funding sites all around the country that will hopefully move the needle in terms of these numbers. That's what Congress wants to see. They want to see us improve the

situation, so we've taken the $30 million that they've appropriated and delegated it in different ways. For example, we built upon what we learned with the RADx-rad initiative and how you can use technology to address a need. We initiated a challenge in which we asked companies to tell us how they are going to recognize problems in postpartum women. The reason why we selected postpartum women is maternal mortality includes up to the year following delivery. In fact, more than half of the women who are dying are dying after delivery. We also thought that if we are going to commercialize technology, it's a lot easier to do that in a non-pregnant person than a pregnant person. We now have a challenge. We are down to the ten groups that are implementing their technology. We started with a large number. It's a funnel like they had for RADx-rad. We started on a large group and now the groups have competed. We're down to the top ten. At each stage in the competition, they receive prize money. The technologies that are being studied include ways of detecting postpartum hemorrhage, for example, and ways of detecting mental health issues. They are largely directed towards rural areas or underserved maternal areas, where people can use their smartphones and problems that can be recognized, and then they can be referred for help. A huge issue right now are the so-called maternity care deserts, which are areas in the country where there are no qualified obstetric providers and women don't have access to care.

The other part of the IMPROVE Initiative, in addition to the Centers of Excellence and the technology approach, is the community initiatives where we are working with individual communities based on trusted relationships. The communities are telling us what they need. I participated, for example, in a tribal consultation in which members of different American Indian communities told us what they needed. Those conversations indicated what the different needs were, whether it was access to nutritious food or transportation to get to prenatal care. There are a lot of things that, living in Bethesda with access to care, we wouldn't necessarily be thinking about. We need to hear it directly from the affected communities. We're very excited about the IMPROVE Initiative and we're looking forward to really making a difference in this area. It's so important this issue doesn't go away. We've heard a lot about, for example, Olympic female athletes who died during pregnancy or postpartum due to conditions that are treatable, but they didn't recognize their symptoms or they didn't get access to care. We're very passionate about this subject and we're very dedicated to making a difference here.

Barr: Is there anything else that you would like to share about NICHD's pandemic experience or even your own? You're an individual as well as a physician and a scientist.

Bianchi: Well, I'm a physician and a scientist and a person too. We talked a lot about NICHD and the Institute's experience and our staff and the changes. One big change is we have a large number of people who are working fully remotely now from all different parts of the country. I often joke about "NICHD West" because we have a lot of people in Colorado and California. They are Zooming in like the rest of us, but they're permanently elsewhere. I think that has had pluses and minuses, but it certainly has allowed us to recruit hugely talented people that we wouldn't have been able to do otherwise. We're grateful that they've joined us and hopefully they will stay with us.

From a personal perspective, I am one of the commuting IC directors. About a third of us commute—including Dr. Monica Bertagnolli, by the way—back and forth from another location. At the start of the pandemic, I didn't want to leave Bethesda because I felt responsible for our staff in the area. I felt that I needed to be physically present for whatever happened, to be able to roll up my sleeves and participate actively in all of the discussions. What that meant was I was living alone, separated from my family in my work apartment here in North Bethesda. . It was difficult personally because I couldn't go home. I didn't want to travel. After about three months, when we had a better sense of what was going on, I finally

drove home, but had no interest in flying, which is how I usually commute. In addition, I have my own research laboratory, which we talked about in the previous part of this conversation, and I felt very responsible for people in the lab who for the first few months were working from home. We have a clinical research project ongoing, studying pregnant people from all over the US who may or may not have cancer. They didn't want to come to the NIH during the early stages of the pandemic. But the postbacs, the trainees, who came with the expectation of being able to do great things at the bench—that was a serious problem. We didn't really talk in great detail about the trainees at NICHD, but there's a whole generation of scientists or would-be scientists whose career plans have been affected by the pandemic, particularly women with children. I was very concerned about people in my lab and their mental health and their experiences. I think ultimately everyone did all right, but there were periods of time when some trainees had mental health concerns.

Barr: Well, thank you very much for all you do and all you've done. I wish you and NICHD only the best going forward.

Bianchi: Thank you very much, Gabrielle, and maybe we'll have a chance to speak again.

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