This interview was supported by a donation from the American Academy of Pediatrics Section on Clinical Pharmacology and Therapeutics
PREFACE

Oral history has its roots in the sharing of stories which has occurred throughout the centuries. It is a primary source of historical data, gathering information from living individuals via recorded interviews. Outstanding pediatricians and other leaders in child health care are being interviewed as part of the Oral History Project at the Pediatric History Center of the American Academy of Pediatrics. Under the direction of the Historical Archives Advisory Committee, its purpose is to record and preserve the recollections of those who have made important contributions to the advancement of the health care of children through the collection of spoken memories and personal narrations.

This volume is the written record of one oral history interview. The reader is reminded that this is a verbatim transcript of spoken rather than written prose. It is intended to supplement other available sources of information about the individuals, organizations, institutions, and events that are discussed. The use of face-to-face interviews provides a unique opportunity to capture a firsthand, eyewitness account of events in an interactive session. Its importance lies less in the recitation of facts, names, and dates than in the interpretation of these by the speaker.

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ABOUT THE INTERVIEWER

Kathleen A. Neville, MD

Dr. Neville is board certified in pediatrics, pediatric hematology/oncology and clinical pharmacology. She received her Master of Science degree in Clinical Research from Indiana University. She has clinical trial expertise (e.g., study design, execution, and data analysis) as well as translations research experience as it relates to pharmacology and pharmacokinetics associated with several drugs including hydroxyurea. She serves as Chief for the Section of Clinical Pharmacology and Toxicology and Director for the Experimental Therapeutics program at University of Arkansas for Medical Sciences/Arkansas Children’s Hospital.

Dr. Neville led the NIH-sponsored Pediatric Trials Network study of hydroxyurea. In addition, she has served as Chair for several national early phase protocols in pediatric hematology/oncology. She also currently serves as Chair of the American Academy of Pediatrics Committee on Drugs and she serves as a consultant regularly for the Food and Drug Administration (the Pediatric sub-committee of the Oncology Drugs Advisory Committee, the Pharmaceutical Science and Clinical Pharmacology Advisory Committee, and the Pediatric Advisory Committee).

Her research interests relate drug development and the early phase (Phase I/II) study of medications in children, characterizing the determinants of variability in drug disposition and response, and development of pediatric appropriate formulations.
Interview of Ralph E. Kauffman, MD

DR. NEVILLE: This is Dr. Kathleen Neville. This is an interview of Dr. Ralph Kauffman conducted by Dr. Kathleen Neville on September 14, 2015. We are in Ann Arbor, Michigan.

So, Ralph, it’s great to be here talking with you. It’s an honor. I think this is a very exciting project. Let’s just dive in.

In the end, we’ll summarize the most recent events of where you were, which was Children’s Mercy hospital [Children’s Mercy Kansas City], and how we met. But let’s start with telling me a little bit about where you were born, your parents, growing up, and your family life as a kid.

DR. KAUFFMAN: I was born in a small town in Colorado, out on the ranch country in south-central Colorado, a town called La Junta, which was the county seat of Otero County, and still is. At that time my father owned a Texaco station in the small village, Cheraw, where we lived 12 miles from La Junta. Some of my earliest memories are walking from where we lived and sitting around his station, while the guys hung out there and talked and teased me.

When World War II came, and gas rationing came, my father decided to get out of the oil business and sold his station and went into farming. He farmed for probably the next 15 years. So, I grew up on a farm in Colorado, and then later in Idaho, southern Idaho.

DR. NEVILLE: Were you around when he had the gas station?

DR. KAUFFMAN: I was a toddler, a preschooler, then.

DR. NEVILLE: So, you remember a little bit?

DR. KAUFFMAN: I have very early memories of that. But most of my memories are growing up on the farm and riding a tractor when they were cutting hay and cutting grain and milking cows and feeding calves and things like that.

DR. NEVILLE: Any brothers and sisters?

DR. KAUFFMAN: I have 2 sisters younger than I am. The one next younger than me is 3 years younger. The other one is 6 years younger than me.
DR. NEVILLE: Describe what you recall from your childhood. Were there lots of family around, or was it hard with farming? What do you remember?

DR. KAUFFMAN: We lived in a community where I grew up with a lot of cousins and uncles and aunts around. I had one particular cousin about my age. Our dads both farmed on land close together, so we played back and forth. Neither of us had a brother, so we were sort of the brothers that we didn’t have. So, that was nice. And I grew up around other cousins, so we got together on holidays for sure and saw each other frequently.

DR. NEVILLE: What do you think were the events in your childhood that led you to start thinking about a career in medicine?

DR. KAUFFMAN: I don’t know. I don’t remember a specific event. But I do remember when I was approximately 9, 10, 11 years old already being attracted to medicine and talking about it with my parents. One event that occurred that probably triggered my interest in medicine was when I was about 11 years old. Working out on the farm during the summer, I sustained about a second- to third-degree sunburn on most of my torso. I ended up making treks into the local family doctor on a daily basis for bandaging in hot July. That made an indelible impression on me. I was very impressed about how he took care of me. So, I remember that as an event. It was one of those experiences in which you have some interaction with a physician and it makes an impression. I know that by the time I was in high school, I had a pretty good idea I wanted to do something in medicine, and by the time I entered college, I knew for sure I wanted to go to medical school. It was kind of a transition during my growing up and teenage years.

DR. NEVILLE: Was there anything else you considered? It had to be hard if your family was in the farm business—or maybe it wasn’t—to leave all that behind for medical school. Were there any other doctors in the family? Were there any other career choices you thought about?

DR. KAUFFMAN: Not that I recall. I for sure didn’t want to feed any more turkeys or calves or ride the tractor anymore. I had no interest in farming at all. [Laughter] No, by the time I was in college, I don’t recall considering any other options. If I would not have been able to go into medicine, I would have had to totally rethink my life because I didn’t have a plan B.

DR. NEVILLE: Was it always understood as an expectation of your parents that you would go to college? Were you the first one in the family to go to college?
DR. KAUFFMAN: No, I wasn’t the first one. My dad had a master’s degree and taught school after he quit farming for 25 years. It was just assumed. We didn’t even ask the question. It was assumed I would go to college—and my sisters, too. It wasn’t a question.

DR. NEVILLE: I’m assuming you’re one of the first doctors in the family. Is that a correct?

DR. KAUFFMAN: Yes.

DR. NEVILLE: So your parents must have been thrilled about that, or maybe not?

DR. KAUFFMAN: They were very supportive and certainly didn’t object to it. I think they were supportive with whatever I wanted to do, as long as it was reasonable. I think they would have supported me in a variety of things. I remember it as my choice, and they supported that choice. My father’s oldest brother, who died before I was born, entered medical school at the University of Colorado, but was never able to pursue it because he died at 24 years of age. He drowned in an accident. So apart from him, I was the first one to go into medicine.

DR. NEVILLE: When you were in high school, what do you think, in looking back, attracted you to medicine? Was it the biology piece of it?

DR. KAUFFMAN: I think I was always interested in biology much more than chemistry. And I think I was attracted by the human side, human interactions, as well as the pure biology of it. But the natural sciences always intrigued me, and even more so in college.

DR. NEVILLE: Where did you go to college?

DR. KAUFFMAN: I graduated from Bethel College. It is a small liberal arts college in Newton, Kansas. They had a very strong premed program at the time, and it was convenient. So, I went there and majored in biology and minored in chemistry.

DR. NEVILLE: So, you went there from Colorado?

DR. KAUFFMAN: We moved. My parents moved to Kansas after my dad quit farming.
DR. NEVILLE: So, you were still a far way away from home?

DR. KAUFFMAN: Oh, yes, yes.

DR. NEVILLE: Tell me again, a major in biology?

DR. KAUFFMAN: I majored in general biology and had a minor in chemistry. I selected those majors with medical school in mind. I certainly didn’t have to do other than the minimum science to apply to medical school, but that was my choice.

DR. NEVILLE: When I applied, I had taken time off. It was pretty competitive. Even undergrad was competitive, because you knew you were competing for limited seats in medical school. Was it like that? Do you recall how you felt during college?

DR. KAUFFMAN: I felt totally intimidated in applying. You can probably share that feeling. I applied, and I don’t know why, but I only applied to that one medical school. That’s unheard of today. But I did. I remember that my dad drove me to Kansas City for my interview at the University of Kansas. He was very supportive, but at the same time, I think intimidated, also. He thought it was a long shot. I had my application in, I did my interview, and I actually got early acceptance that fall.

DR. NEVILLE: Holy cow.

DR. KAUFFMAN: I lucked out. So it all worked out very well.

DR. NEVILLE: That’s fantastic. Let’s talk a little bit about medical school. It seems you went full circle, right? Medical school in Kansas, and then retiring from Children’s Mercy and all that. What do you think shaped you in medical school to start heading toward pediatrics? I’m guessing the basic sciences, although with technology and how far science has come, it’s a little different. Did you love everything? Did you always know it would be pediatrics? How was that for you?

DR. KAUFFMAN: I was like most medical students. You go in and you like everything. Some people know exactly what they want to do, but I wasn’t one of those people. I enjoyed everything. I don’t think I really made up my mind about pediatrics until I was well through my junior year. I enjoyed my pediatric rotation, but I enjoyed surgery and the other stuff, too. But pediatrics, I did enjoy. The thing that really sealed it was my rotation on internal medicine at the VA [Kansas City VA Medical Center]. I said, “I’m
not going to do this the rest of my life.”

DR. NEVILLE: Yes, I remember that rotation. [laughter]

DR. KAUFFMAN: By the time I entered my fourth year, I was pretty much settled. Well, I had to be because I had to start thinking about where I was going to do it.

DR. NEVILLE: Tell me a little bit about your residency, Ralph.

DR. KAUFFMAN: Very few people at that time were going directly into specialized residencies. Some people did, but most people were doing a rotating internship, and then doing a residency after their internship. I ended up doing a rotating internship at the Kansas City General Hospital (Now the Truman Medical Center, teaching hospital for the University of Missouri – Kansas City School of Medicine). I enjoyed it immensely. That year, I did OB [obstetrics and gynecology], I did general surgery, I did internal medicine, and I did pediatrics. It was so different from what it is today because we took a lot of responsibility as rotating interns. It scares me now to think what we did. On my pediatrics rotation that year, I put my first chest tube in a preemie all by myself one night.

DR. NEVILLE Wow!

DR. KAUFFMAN Yes. It was a considerably different world then from what training is now. So, I did a rotating internship, but it served me extremely well. A part of my rotating internship was a rotation on plastic surgery. We spent one afternoon a week doing nothing but minor skin surgery.

[Phone rings — break in audio]

DR. NEVILLE: I want to talk again about your rotating internship because that was different from the educational structure now. You talked about the different rotations and how that served you and maybe further developed your career. I want to get in a little bit of detail about that.

DR. KAUFFMAN: I don’t know if it contributed directly to my future career decisions, but I always viewed it as an excellent general background to what I ended up doing later on. A number of people at that time did rotating internships instead of a specialty internship, and then did their specialty after that. That was what I ended up doing. I had no particular direction then, except I was pretty sure I was going to go into pediatrics, but I hadn’t made
up my mind. Because I planned to go into pediatrics, I did a lot of non-pediatric rotations during that period. We were able, at that time, to take a lot of responsibility, probably more than we should have at times. So, I was able to do a lot of hands-on medicine, surgery, and OB, in addition to pediatrics, during that year, and benefitted from it at various times subsequently.

One example is that during my fellowship, I did a locum tenens for a month down in rural West Virginia for a pediatrician who was on vacation for 2 weeks. I had no specialty backup during that time. I was it. I had a girl who came in the emergency room one night who had been hit by a car while on her bicycle. She had a finger fracture, clavicle fracture, and a nondisplaced pelvic fracture. I had no orthopedic or surgical backup, so I took care of her and she recovered successfully.

DR. NEVILLE: Wow, that’s impressive.

DR. KAUFFMAN: A lot of it was luck, but at least I had some idea of what to do.

DR. NEVILLE: That’s impressive.

DR. KAUFFMAN: I wouldn’t have been able to do that with a straight internship in pediatrics.

DR. NEVILLE: I think the year was 1966, if I’m correct. Can you give a sense, because medicine has changed so dramatically, of what a day in your life was like? How long did you work? Were you married yet? Did you sleep at the hospital?

DR. KAUFFMAN: You mean during my internship in 1966?

DR. NEVILLE: Yes.

DR. KAUFFMAN: My wife and I had been married approximately 3 years, and we had a newborn infant. Our daughter, our oldest of the 2 children, was born a week after I graduated from medical school. She was a baby in her first year during my internship. My hours varied with the rotation, but I was essentially on call every third night, and there were no work-hour limitations then, of course.

When I was on call, I worked 36 hours. I’m not necessarily in favor of that. That was just the way it was. On my emergency room rotations, I was 12
hours on and 12 hours off for the whole month, so it was pretty grueling. And it limited the time with family. My wife was working full time as a nurse at that time, too. We had a busy life with 2 full-time jobs, the demands of an internship, and a new child.

DR. NEVILLE: Do you remember the salary of an intern then, approximately?

DR. KAUFFMAN: My take-home was around $75 a month, so we lived on my wife’s salary. Interns did get snacks at night.

DR. NEVILLE: Wow! [Laughter]

Let’s talk a little bit about your residency. The rotating internship was in Kansas City, what has now emerged as basically another county hospital. Tell me about your residency. It sounds like you already knew pediatrics. Where did you do it? How did you choose? Let’s talk about what that was like.

DR. KAUFFMAN: To talk about that, I need to back up a little bit and tell you what happened during the 2 years between my internship and my residency. I finished my internship at the peak of Lyndon [B.] Johnson’s Vietnam War build-up, so we were all in the draft. They were deferring physicians through their internship, but then they had to go in if they weren’t in what was called the “Berry Plan.” This was a provision as part of the Selective Service at that time for physicians [to fulfill their military obligation] if you were accepted for what was called the Berry Plan. It was named after one of the congressmen who sponsored the law [first established during the Korean War by Frank Brown Berry, the Assistant Secretary of Defense, Health and Medical]. If you weren’t in the Berry Plan, you went into military service right out of your internship. If you were in the Berry Plan, the military would defer you for at least part of your residency, if not your whole residency, but then you had to pay back year-for-year in active duty after that.

I and all my colleagues were slated to be drafted the minute we finished our internship, so early that year, a number of us went down and applied for US Public Health Service uniform corps commissions [Commissioned Corps of the US Public Health Service]. I was one of the lucky ones selected for that. I thought I was going to be doing medical care for the [United States] Coast Guard, but unbeknownst to me, there was an agency called the FDA [US Food and Drug Administration]. Also unbeknownst to me, the then-commissioner of the FDA had made a deal with the Surgeon General to assign 60 Public Health Service officers to the FDA to help them with their
workload because they were just starting to implement the 1962 Drug Amendments [Kefauver-Harris Drug Amendments to the Food, Drug and Cosmetic Act of 1938, passed October 1962, implemented June 20, 1963]. So instead of going to the Coast Guard, I got sent to work at the FDA for 2 years. When I came back to my residency in 2 years, everyone thought I knew something about drugs, but I didn’t really. I knew a lot about food and drug law, but I didn’t know much about drugs. It was an excellent experience for what I ended up eventually doing.

DR. NEVILLE: Yes. Tell me more about that and the details of what you did in those 2 years.

DR. KAUFFMAN: About the FDA?

DR. NEVILLE: Yes. When you look at the FDA now—we’ll get to it much later—I think we take a lot of the guidances and legislation for granted now because we have things like the 1962 amendments and what came around in the 1960s and 1970s. You were a part of that. So what did you do there and what was it like?

DR. KAUFFMAN: It was an amazing experience, because we walked into the FDA 3 years after the 1962 Drug Amendments had been passed. This law, as you know, provided a number of things, but one of the biggies was that it required companies to do clinical studies to provide proof of efficacy, as well as safety, before drugs could be marketed. The FDA had never had the expertise or the personpower to do that in the past, and they were frantically gearing up to handle this onslaught of big, massive new drug applications that included all of this data, plus implementing the new regulations. Then there was a whole backlog of previously approved drugs that had never been studied to show efficacy and had to be grandfathered. There was a separate process under the law to deal with those, but it took years to go through that, too.

There were 60 of us selected from around the country to go do this. We went to the FDA, a bunch of green, fresh out of medical school and internship doctors. They gave us a 2-month orientation in what was then food and drug law and procedures. Some of us were assigned to work on what was called the DESI [Drug Efficacy Study Implementation] review. It was reviewing some of the older drugs. The bulk of the people in the group were assigned to review new drug applications under the new law and regulations. I and one other public health service officer were assigned to the division of labeling and medical advertising [Advertising and Promotional Labeling Branch], which was a whole new world.
We all have had, at various times in our training and careers, exceptional people who were influential and mentored us. One of the people who was that for me was the head of this division, Dr. Robert McCleery. He was a former surgical faculty member at the University of Minnesota and was now heading up this new division at the FDA. There was also a pharmacist lawyer in the division right under him named Harry Chaduck, who was the lawyer for the division. They took me and the other [US] Public Health Service officer under their wings. In the next 2 years, I learned more about food and drug review approval and food and drug law than most physicians even know exists. It was invaluable down the road when I finally ended up in clinical pharmacology. It was an amazing experience. The thing I didn’t like about it was that I had very limited clinical exposure during those 2 years. I really missed that because I was at the point in my career when I really wanted to be doing clinical care. But in retrospect, it was valuable.

We were in charge of reviewing the labeling for new drugs that were coming through approval to make sure that they complied with the law and the data that was supporting their approval. Also, under the law—and this is still true—all of the promotional materials on a drug have to be consistent with the labeling. So, it was our responsibility to police the advertising programs for new drugs coming on the market, too. I had several experiences where we actually had new drugs approved, and the companies had their drug in the pipeline, and then they came out with their labeling and their promotional materials that were in flagrant violation of the law. I ended up a couple times in the commissioner’s office participating in activating embargoes on these drugs until the companies complied and sent out “Dear Dr.” letters across the country to correct the infraction.

DR. NEVILLE: That’s incredible.

DR. KAUFFMAN: It was incredible that at 26, 27 years of age, I was sitting across the table from some of these company officials and engaging in these debates and negotiations and so forth.

DR. NEVILLE: And this was new for them, right, the enforcement of this? So, of course, they were pushing the envelope.

DR. KAUFFMAN: The FDA was plowing new ground completely and finding their way. They were still coming out with guidances. The regulations were new, but they were still creating guidances. The companies were certainly finding their way in this new legal landscape. It was an amazing time to be involved in that.
DR. NEVILLE: Especially since you and I both know that, largely, the label is the tangible product of the FDA, right?

DR. KAUFFMAN: Right.

DR. NEVILLE: That, it sounds like, was the first iteration of the label.

DR. KAUFFMAN: Well, no. There had been labels previously. But the labels now had to be much more detailed, differently organized, and include efficacy information. The critical thing was that medications could only be indicated and promoted for indications for which they had been legally approved. This caused a lot of confusion and consternation and problems for both the agency, as well as the company sponsors.

DR. NEVILLE: I should qualify and say the label as we know it. You look at old advertising for this tonic and that drug, and then all of a sudden they were held to a standard of proof, right?

DR. KAUFFMAN: We’ll need to come back to this further at the end of the interview, because this is the crux of the problem that was created inadvertently for children down the road, that then we all dealt with for 40 years. But we can come back to that later.

DR. NEVILLE: Going into it, you knew it was going to be 2 years, right? Two years, you’re done, you get to go to residency.

DR. KAUFFMAN: Yes. The conscription requirement was there, but you had 2 years of service. I knew I was going to go back and enter a pediatric residency someplace.

DR. NEVILLE: Did you know from the time you went that you would go back to Kansas, or how did you pick a residency?

DR. KAUFFMAN: Not for sure, but one of the big influences was that my wife’s family lived near there, and we owned a house in Kansas City by then, so there were a lot of draws. Then I was heavily recruited by the University of Kansas Department of Pediatrics to come back and do my residency there. So, it was a comfortable thing to do, and we ended up going back. My wife had a job waiting for her there. In retrospect, I might have looked around some, but it would have been difficult to do otherwise at the time.

DR. NEVILLE: You still had one child?
DR. KAUFFMAN: Just one. Our second child, our son, was born during my fellowship.

DR. NEVILLE: So, tell me about residency. Was it what you expected? You and I have talked about this before, how different it was back then compared to the residency experience now. I think, as part of this history, I want people who are reading it in the future to get a feel for what it was like and how what it was like influenced you.

DR. KAUFFMAN: I think, in many ways, it wasn’t unlike what people do now in their residency. We had our inpatient rotations, neonatal nursery, general pediatric floors, infectious disease, and then specialty rotations and outpatient rotations. So, in that sense, I don’t think it was that different, rounds and teaching rounds and so forth. I think one thing that was maybe somewhat different from now was that we, of course, didn’t have HIPAA [Health Insurance Portability and Accountability Act of 1996, Public Law 104-191] constraints. It was all paper records. We didn’t have electronic medical records.

DR. NEVILLE: And you didn’t really have the internet as an information source, right?

DR. KAUFFMANN: There was no internet. I still have the mini slide rule I carried in my pocket to calculate doses on pediatrics. We didn’t have the little, small electronic calculators yet. They came a few years later. Other than the tools we had, the medical information we had, some of the medications that we have, and the way we use drugs, it was very similar. We didn’t have a lot of the vaccines we have now, so we saw diseases that the residents no longer see. We saw a lot of measles and pneumonia. We saw rubella, encephalitis, blindness, mental retardation, horrible H-flu [Haemophilus influenza] meningitis, meningococcal meningitis.

DR. NEVILLE: Pertussis. Did you see pertussis?

DR. KAUFFMAN: We didn’t see pertussis, really. At least I didn’t. Different from what people see now in unvaccinated kids or infants, because pertussis vaccine and polio vaccine were there long before that and so were the DTP immunizations [DTaP - diphtheria, tetanus and pertussis vaccines]. Then measles and rubella [vaccines] came in shortly after my residency. But during my residency, we did see a fair amount of that kind of thing.
DR. NEVILLE:  And H-flu meningitis, I don’t think even I’ve ever seen it in my career, and I’m told it was terrible.

DR. KAUFFMAN:  H-flu meningitis and meningococcal meningitis were devastating, and we saw a fair amount of it, particularly during the winter.

Residents didn’t have the constraints on work hours, so my first year, we typically, again, took call every third night. Then on outpatient we had much less frequent call, so those were viewed as easier months. During our second and third years, of course, we did a lot more subspecialty rotations and fewer call nights and things like that. So, it was very similar to what you have now, except, again, we were up 36 hours, usually, on the 2 days that overlapped when we were on call. The first year was pretty grueling because we didn’t really ever get rested up from the previous 36 hours before we had to hit it again on that kind of a call schedule.

DR. NEVILLE:  It struck me—and tell me whether you agree or not—that it was quite grueling, but I think you got to see patient from the beginning to the end, so young in your career, the patient identified you as their doctor. Do you think that was the case?

DR. KAUFFMAN:  Yes. We did that, particularly in outpatient and resident clinic, but also in-house on the inpatient service. We did see them through their entire hospitalization. We didn’t have the sense that we were working on a shift. I’m not sure that’s the best, but it was the way it was at the time. We were acculturated to view medicine that way—that we were obligated to stay with a patient or do whatever was required and see it through. Sometimes we were probably too tired to do an adequate job, but that was the way it was done then. I think then we were given a lot more direct patient responsibility than the residents are now because we didn’t have all of the legal pressure and Medicaid and insurance company rules during my residency. There was insurance, but we didn’t have all the rules that we struggle with now. The faculty was never there at night. The most we could hope for was to get them to answer the phone.

DR. NEVILLE:  Ralph, what was the workforce like back then? Such as in your resident class, men and women, was it an equal split? Mostly men? Mostly younger? Your age? Can you comment on that?

DR. KAUFFMAN:  I think all the people in my residency class were my age and had graduated about the same time. The women were approximately 2 years younger than the guys. The guys had all been in the service before, and then done the residency. The girls weren’t in the service. But we had
essentially graduated the same time, within a year or 2 of each other. It was a majority of males and a minority of females. Out of my medical school class of 110, there were only 10 women. Now it’s 60% women, 40% men, so there has been a big change in that. But yes, at that time, it was still predominantly males, even in the pediatric group. I don’t remember exactly how many women we had versus guys [in residency], but it was a majority of men.

DR. NEVILLE: I think we forget now what it was like without the internet. When you had a perplexing case come in, what did you do? Where did you go for information? I have a vision of the resident sitting up all night, grabbing books, reading. Right now, it’s a couple clicks of a button. How did you approach that?

DR. KAUFFMAN: The library was open and available 24/7 for us. We had handbooks that we carried in our pocket all the time that contained the everyday electrolyte stuff, drug doses, starting drug doses, and basic stuff like that. Typically, we would go to the library and start pulling current textbooks off the shelf. Beyond that, it was going to the Index Medicus volumes and manually looking through them and doing laborious literature searches. We didn’t do that, except for the rare complex patient, but you could spend 2, 3, 4 hours in an afternoon with the Index Medicus, trying to get a literature search pulled together. Now you can do that in 15, 20, 30 minutes. So, it was a very different world.

The other thing I think we were taught differently was how to seek and assemble information about the patient and translate it into a treatment plan or a management plan. I think some of that has changed because of the instant information at the bedside and the access to instant diagnostic algorithms and so forth available now. We were taught to do it a different way, but essentially, fundamentally, the same approach. I think we spent more time in taking detailed histories and writing out a detailed differential diagnosis, then a working diagnosis, and then supporting or not supporting that. But as you know, even in inpatient pediatrics, there are 15, 20 conditions that comprise 90-something percent of your patients, so you develop best practices for taking care of those. In those cases, it wasn’t that different, except the fount of information was different from what it is today.

DR. NEVILLE: I’d be interested in your perspectives of what neonatal medicine was like then and what the nursery was like then. We have [Micromedex] Neofax and we have premature infants surviving earlier—I think a lot of things my generation and the generation after me take for granted. It had to be, just like it is now, but in a different way, tough at times to rotate through the nursery then.
DR. KAUFFMAN: Well, it was. Where I was, we didn’t have anything that would resemble a tertiary or quaternary neonatal ICU [intensive care unit] today because they didn’t exist like that 40 years ago. There was intensive care for neonates, but we didn’t salvage them as small as they are today. If we could get a good outcome on a 1,500-grammer [newborn weighing 1,500 grams], we were pretty happy—quite happy, in fact. The perinatal care wasn’t what it is today for a complicated delivery either. But we did have infusion pumps and we had early ventilators. We intubated. We put chest tubes in. I mean, a lot of the care was the same. We had pressers and fluid therapy. We didn’t have gases as easily as you have. It was a lot harder to get gases on [neonates].

DR. NEVILLE: I bet. I mean, putting a chest tube in had to be incredible.

DR. KAUFFMAN: Of course, we didn’t have the imaging that you have today either, digital imaging.

DR. NEVILLE: I maybe should know this but I don’t because I am of a different generation. What did you do about dosing? I’m guessing you saw a fair bit of congenital infections. How did you dose neonates?

DR. KAUFFMAN: Neonates, oh, by gosh and by golly. There was very little to go [on]. It was subsequent to that that people like Sumner [J.] Yaffe and [Robert] “Butch” Roberts and others tried to work out and develop doses for neonates. As you know, we still struggle with that today. But some of the earliest recommendations and doses that were used were from those 2 individuals and others who were trying to develop them. A lot of it was just not based, really, on data. It was experience, and some of it was very bad. There’s a whole litany of therapeutic misadventures in the newborn that you’re aware of, and others are too, that happened because we didn’t know what we were doing in newborns, as well as older children. So, we used what we had, but we found out later that some of what we were doing was not correct. It was gradually corrected with experience. But a lot of the doses were simply developed by extrapolation, and then experience. “We got by with this, so you can, too” kind of logic.

DR. NEVILLE: Which I think is a good segue. So, you did general pediatrics. What got you interested in clinical pharmacology?

DR. KAUFFMAN: Well, this was one of the unplanned twists. I don’t know if most people have that happen to them, but this was really an unplanned twist in my career. It started with being sent to the FDA, but I didn’t realize it at the time. As I said, when I came back to do my pediatric residency,
people thought that because I’d been at the FDA for 2 years, I should be an 
expert on drugs, which I wasn’t.

So, I was enjoying my pediatric residency. Right up to late in the second year 
of my residency, I had planned to go into general pediatric private practice. I 
was even looking around the country at potential practice sites. Late that 
year one Thursday, Dan [Daniel L.] Azarnoff called me in. Now, I need to 
give you a little background. Dan Azarnoff was the head of the Clinical 
Pharmacology [and Toxicology] Center at the University of Kansas [Medical 
Center] [now, the Department of Pharmacology, Toxicology, and 
Therapeutics]. He had been, in the mid-1960s, one of the original awardees of 
the Clinical Pharmacology and Toxicology Center grant from National 
Institute of General Medical Sciences, NIGMS. They had funded 6 centers 
around the country, all in adult departments. Dan called me in one day and 
said that he had an NIH [US National Institutes of Health] training grant 
available if I wanted it, and I just said, “Tell me more about it.” He had a 
deadline and he needed to know by the first of the next week if I wanted it or 
not. Well, this was a whole different change, because if I decided to do that, it 
was a selection, essentially, to go into academic medicine, to go into a 
research-based career that I hadn’t really anticipated, and to do something 
very different from what I’d planned to do. But I thought about it and 
decided to do it, and that was a 180-degree change in my career plans at that 
point.

DR. NEVILLE: So, it also had to be one of the first pediatric pharmacology 
fellow slots.

DR. KAUFFMAN: I suspect so, because at that time, to my knowledge, there 
were no pediatric training programs in the country. Dan had a lot of trainees 
from Europe, including Scandinavia, as well as the US, but I was the first 
pediatrician he took on as a trainee. He really didn’t know what to do with 
me.

DR. NEVILLE: Ralph, do you think it was your experience as a resident 
with not knowing dosing? What do you think it was? Because that, like you said, 
is a big shift, right?

DR. KAUFFMAN: Yes, it was a big shift. But I thought about it and I 
realized I had this experience at the FDA, which was unique for most 
physicians, early in my career. And this was a unique opportunity at the front 
end of a specialty that really didn’t exist to any degree. Even the internal 
medicine people were struggling to figure out what this should be at that 
time. But they had at least convinced NIGMS to fund some large centers,
which included training grants for those centers. I thought it was intriguing and I thought it might be really an exciting career. But I felt like I was a kid on the 25-foot diving board, holding my nose and jumping off, too.

DR. NEVILLE: I bet.

DR. KAUFFMAN: But I did it. And we were able, with the chair of pediatric’s help, to convince the American Board of Pediatrics to let me combine my last year of pediatric residency with the first year of my fellowship and condense one year off of my total training. That helped me, too. So, I ended up doing a full fellowship in clinical pharmacology with Dan Azarnoff.

As I said, he wasn’t sure what to do with me, except he had an excellent training program, and so I not only attended the graduate classes in pharmacology and their seminars and so forth, but he set me up with what I needed in a laboratory. My biggest struggle was deciding what research area to pursue, because I didn’t fit into any of his niches. I really had to come up with something that was mine. One of my real struggles was that I didn’t have a good pediatric mentor in that discipline [clinical pharmacology] to help me identify problems or to do it. Dan and the faculty in that center were superb at helping me with laboratory techniques and basic pharmacology and so forth, but they didn’t have a clue what needed to be done or what I should pursue in the area of pediatric medicine. So, I struggled a little bit the first 6 months with trying to work that out.

DR. NEVILLE: I wonder—again, things we take for granted—were there even pediatric mentors out there?

DR. KAUFFMAN: Not in pediatric pharmacology. Well, there were a couple people who were already doing this. I shouldn’t say there was no one. Sumner Yaffe was a young faculty member at Stanford [University]. He was doing some amazing things there as a neonatologist, and getting into pharmacology.

The other person who was a real influence—and we can get into this later if you want to—was Harry [C.] Shirkey, who at that time, I think, was chair at Alabama, but then he went to Hawaii, and by the time I finished my fellowship, he was the chair at Tulane [University School of Medicine]. He had written the original pediatric therapeutics textbook [Pediatric Therapy] and carried it through about 6 editions during his career. His first or second edition was out by then, and he was very prominent in that area. So, those were 2 people who were sort of role models at that point. They weren’t
located where I was, but I knew about them,

DR. NEVILLE: Which makes it hard.

DR. KAUFFMAN: I was very fortunate when I came out of my residency. Dan Azarnoff was able to provide me funding, so I spent the first year of my fellowship really learning basic research methodology and technique. I did a couple of adult clinical studies to learn what it was all about. We had a clinical research unit there, so I was able to do them in there. Then my second year of fellowship, he helped me get a couple of drug study contracts for pediatric studies with drug companies. One of the earliest studies I did was during the second year of my fellowship. I studied the pediatric pharmacokinetics of one of the new antistaph \textit{[Staphylococcus aureus]} antibiotics. I think it was dicloxacillin—I don’t remember for sure. I was able to publish that. One of the interesting things about that was that when I came up with the data, the company thought I had made some major errors because the clearance in the kids was so much greater than the adult studies they had. They thought there was a big mistake someplace. [Laughter]

DR. NEVILLE: Which is amazing. For me, as I said earlier, it’s an honor to sit here, because all of these things that we take for granted as basic knowledge now were just unknown, right?

DR. KAUFFMAN: Yes, right. It was a whole new world, pretty much. There were a couple of people around who were starting to advocate for and starting to do studies in kids, but there were no training facilities, and it was very rare to find anyone in pediatrics who identified themselves as a clinical pharmacologist. There were a few people who were interested in therapeutics, pediatric therapeutics, which was a little different concept at the time than pharmacology, per se.

But back to the FDA. I know we’re jumping around.

DR. NEVILLE: That’s OK.

DR. KAUFFMAN: I started telling you about Dr. McCleery, Bob [Robert S.] McCleery, who had been at the University of Minnesota, and was then head of the division I worked in [at the FDA]. He was a tough, but wonderful guy to spend 2 years with because he simultaneously gave me an unbelievable amount of responsibility in some of the things we dealt with, but was very demanding and instructive. He was one of the people, and not the only one, but one of the people in my life who taught me how to write. I mean, he was really excellent, but very demanding. And I’ve always appreciated that.
DR. NEVILLE: Well, it served you well, obviously.

DR. KAUFFMAN: Yes. The other person who really taught me how to write was Dan Azarnoff, my mentor, clinical pharmacology mentor, because he was equally demanding. I mean, nothing went past him without at least 6 total revisions, and usually more. And he was merciless. In those days, we didn’t have word processing, and a lot of my manuscripts were written out longhand, and then typed by someone. We had typewriters that were self-correcting and were programmable so that once you got everything the way you wanted, you could hit the button and it would type it, but they were still typewriters. We didn’t have word processing. So, my manuscripts would come back from Dan Azarnoff just marked with red all over, or critical and caustic comments, but very caring. He was a very caring person, but, thankfully, demanding. So, it prepared me well for reviewers when I submitted. I’d already had my skin bruises and abrasions. I didn’t care what the reviewers said. [Laughter]

DR. NEVILLE: It’s funny.

DR. KAUFFMAN: I appreciate that because it made a big, big difference in my academic life with my writing.

DR. NEVILLE: So, you started doing trials and you decided to stay at the end of the fellowship?

DR. KAUFFMAN: I was very fortunate at the end of my fellowship because I finished my fellowship right when Dan was up for his first 5-year renewal of the center, and he invited me to submit a couple of projects for the center. Funding was very different then from what it is now. The funding levels were higher than they are now. But I was able to go in with my first NIH proposal right out of my fellowship as a part of his center grant, and I got funded. So, I had 5 years of funding, plus some other smaller grants I got, walking into the lab. And the pediatric chairman there asked me to stay on the faculty. They set me up with a brand-new laboratory in a new building with a technician and sent me on my way. So, it was mine to fail at that point.

DR. NEVILLE: Clinically, what were you doing at the time? I’m guessing a lot of your time was research. Did you miss clinical practice? How did you balance the clinical and the research?

DR. KAUFFMAN: I have news for you. In my entire 40-year career, I never satisfactorily balanced clinical and research activities.
DR. NEVILLE: That’s not the answer I wanted. [Laughs]

DR. KAUFFMAN: I never did.

DR. NEVILLE: Does anyone ever?

DR. KAUFFMAN: No. It took about 15 to 20 years to realize that I never was going to, but that I had to make choices. But no, during the first 20 years of my career, I tried to do it all. So, I had a lab. I had a technician. We had study nurses. I always had projects going. I had a PMAF [Pharmaceutical Manufacturers Association Foundation, now PhRMA, Pharmaceutical Research and Manufacturers Association] grant and I had some other smaller grants that I was able to get to fund some of the stuff. So, I had funding.

About that time, after I had been on the faculty a year or so, the chairman of pediatrics decided to form a private practice group within the department, so 6 of us organized a private practice part time. We were all part time because we were attending inpatient so many months out of the year, trying to run our laboratories, and then this practice. So, we formed a 6-person private practice and practiced out of the university pediatric clinic there. We hired 6 nurse practitioners to work with us. They worked full time in the practice, and each of us worked part time. We each developed our own patient panel. I did that for probably 5 or 6 years, and it was enormously satisfying and rewarding, and I learned a lot from it. I did that until I moved to Children’s Hospital [of] Michigan at Wayne State University in 1979.

When I moved there, I had to make some choices because I was in a much larger hospital and going to have a bigger obligation to clinical pharmacology. I didn’t do any more outpatient medicine after that. I just did inpatient attending after that. I really always enjoyed clinical medicine enormously, but I could never leave the research alone. To the extent I was able to do clinical trials and combine the 2, that was the best of both worlds, but I wasn’t always able to do that.

DR. NEVILLE: We’re going to talk a little bit later about some of the work you did and the research ethics arena, but what was doing pediatric clinical research like during your fellowship in terms of logistics and requirements and IRBs [Institutional Review Boards] and patients even agreeing? How was it viewed, and what was your experience?

DR. KAUFFMAN: The IRB system was fairly new then, but it was up and
operational. This was in the early 1970s. [At the University of Kansas], we had an institutional IRB, and everything had to go through the IRB. Since it was a university hospital and not a freestanding pediatric hospital, most of the protocols coming through the IRB were adult protocols, so the pediatric ones were a small minority there. I don’t recall any real issues around trying to get protocols approved and so forth. I’m sure I was frustrated at times, but it wasn’t enough that it stuck in my memory. I actually served on the IRB for a few years, and I don’t recall problems there. I think the problems with enrollment were very much like they are today. It depended on what kind of study you were doing. It depended on the approach to the patients. I think one of my frustrations initially was that it was a smaller pediatrics department, so I didn’t have the patient population in Kansas City, at the University of Kansas. I didn’t have the patient population to recruit from that I really felt I needed. That was one of the reasons I moved in 1979 to Wayne State. I could be in a large children’s hospital, and we had a large patient population with a clinical pharmacology, pediatric pharmacology group, so it offered me opportunities that I knew I would never have where I was. I decided, because of that, to move when I had the opportunity. Other than that, I think recruiting for pediatric trials was very much like recruiting today. You talked to the parents, you talked to the children. We had to get complete signed informed consent, and so forth. I suppose the IRB system had been up and running probably for somewhere around 5 to 8 years by then.

DR. NEVILLE: Do you see any differences in it now versus then?

DR. KAUFFMAN: I think the approach to children. I was doing my earliest studies in the 1970s, and the actual guidelines for children in the federal regulations weren’t finalized until 1983. So, we were working without a lot of the ethical guidance that we have right now. But the [American] Academy of Pediatrics Committee on Drugs, the Academy, was already working hard on this and came out with their first ethical guidelines, I think, in the mid-1970s [Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations, 1977]. I don’t remember the date. I was on the committee at that time, so I was able to participate in that effort.

I was exposed to the concepts very early in my career as I was doing some of the work, and that was extremely helpful, too. We were learning, we were arguing, we were debating during those years. That made it somewhat more difficult sometimes with the committee, with the IRB, as well as with some particularly well-educated parents. There were very influential ethicists, one of whom was at the University of Kansas at that time, who thought that no research should involve children. Then there was another side that felt there
was a way to ethically involve children in research if you had the right oversight and the right ethical structure within which to do it. So, we sort of felt our way, and I’m sure made some mistakes sometimes, because the ethical guidelines and ethical structure for including children in research was not nearly as well developed then as it is now.

I lived through a 20-year, 30-year period when we gradually learned, and finally the tide gradually shifted to where I think most of us are comfortable today that there is an ethical way that children can be ethically involved in research. In fact, we really promoted the idea within the Academy of Pediatrics that it was unethical not to include children because children were put at high risk of therapeutic misadventures by not doing the research. But that all evolved over a period of time. In my earliest studies, we didn’t have that insight that we did later on.

DR. NEVILLE: The AAP ethical guidelines, at least now, is viewed as a landmark policy statement. You talk about it evolving. I’m interested in your perspective on what it was like to be on the committee and what kind of reaction there was to that statement when it came out. I think it sounds like it was somewhat controversial and a new thought that it’s unethical to not study children. Tell me a little bit about the environment, if you recall, when that policy statement came out.

DR. KAUFFMAN: I’ll tell you the things that come to mind. At that time—and I don’t know if you still do—the Committee on Drugs had a contract with the FDA that paid for half of our meetings. We actually met 4 times a year, and 2 of the meetings were funded by the FDA contract to provide advocacy and advice, expert advice, on pediatric issues. Then the other 2 meetings were funded by the Academy. So, we met 4 times a year and we met in very nice places. I remember sitting on the beach down in Naples, Florida arguing the ethical guidelines draft. It was very instructive. There was John [M.] Freeman from [Johns] Hopkins [University], who’s a neurologist; Sandy [Sanford N.] Cohen, a neonatologist and clinical pharmacologist; and Syd [Sydney] Siegel, I think. I don’t remember everyone on that committee, but those 2 [John and Sandy] stood out, because they were the ones who had done a lot of study on the guidelines. They provided much of the ethics background for our statement and presented a lot of the basis for our draft. It was extremely instructive for a new member of the committee to sit through that.

Over the next couple years, the draft was finalized. It took at least 3 years to get it finalized, and then finally approved by the Academy. I don’t recall, at least I wasn’t aware, that once it was finalized, it was particularly
controversial, other than a few bioethicists who continued to argue through the years about the specifics. But I think the industry found it extremely helpful, eventually. Not right then, because they weren’t doing many pediatric studies. It became extremely helpful later on during our advocacy for passing legislation to do pediatric studies. It was a step in a long process to try to develop an infrastructure, an ethical infrastructure that would allow us to move forward with this. In 1974, we had actually published a guidance doing studies in children [General guidelines for the evaluation of drugs to be approved for use during pregnancy and, for the treatment of infants and children]. Not ethical guidelines, but it was how to do studies, things to take into consideration to do clinical trials in children in 1974. Then the ethical guidelines followed 3 years later. It was a very instructive thing, and we were learning as we went. It turned out to be a very influential document, and has been revised, as you know, at least twice, if not 3 times, since then, and updated.

DR. NEVILLE: And it’s still cited. I think of it as a landmark document because it’s sort of the origination of what, I think, is now law.

DR. KAUFFMAN: It had a big impact on the 1983 “Common Rule” that is now the regulatory basis for the ethical conduct of research in children.

DR. NEVILLE: I want to shift gears—kind of, but not totally. Ralph, if you had to pick one or a few things, what would you say have been the major scientific advances over the years that have affected pediatrics the most? From this arena, we’ve talked about the information age and general pediatrics evolving and how there wasn’t really any pediatric clinical pharmacology at that time. You were probably the first fellow. In the arena in which you’re an expert, what do you cite as the biggest advances for kids?

DR. KAUFFMAN: In pediatric pharmacology?

DR. NEVILLE: In either pediatrics or pediatric pharmacology or both.

DR. KAUFFMAN: I think I’d have to say the growth of genetics and genomics into the mainstream of pediatric medicine because it has impacted every aspect of pediatric medicine, including pharmacology, and has been the single thing, I think, that has just opened up so many diverse areas of research, as well as knowledge. The advancement of vaccines, I think, has had a profound effect. Vaccines that have been developed over the last 30 years have been extremely important, too, but I don’t think anything has had the impact that the developments in genetics and genomics have had. It’s allowed us to study human developmental biology in a way that was never
possible before.

Second to that, which is really a supporting tool, is data management, which is computing. The genetics and genomics revolution and all the “omics” revolution couldn’t take place without commensurate data management of massive data so that the human mind can understand it. So, I think in terms of research, those 2 things have really been the major things.

I’d have a hard time picking one thing in clinical medicine because there have been so many. It’s such a massive area.

DR. NEVILLE: Yes. Look at technology and how that has advanced. I don’t think of myself as that old, but I remember writing notes. Nothing was searchable. We have Fitbits now and monitors now.

If something comes to mind, we can go back to it.

[Audio break]

DR. NEVILLE: Today is September 15. I am in Ann Arbor, Michigan, interviewing Dr. Ralph Kauffman.

Ralph, at our last session, we left off at the time in your life when you were doing a fellowship and were junior faculty at the University of Kansas. I’d like to pick up the conversation with that. I’d like to talk about some of the projects you did and how you chose them, and go from there.

DR. KAUFFMAN: OK. When I finished my fellowship, I was fortunate because the Clinical Pharmacology Center at University of Kansas was up for 5-year renewal funding through NIGMS, and I was invited to submit a project under that center grant. I elected to submit a project that would study the dynamics of transfer of drugs across the placenta. That was a relatively untouched area, and I thought we might be able to do something there. The grant was approved, and I did receive funding. During the next few years, then, we developed what I thought was a very elegant model in sheep, in which we would operate on the sheep in third trimester pregnancy. One of the attractive things about sheep is that the gestational period is approximately the same as human, and the size of the fetus is approximately the same as a human. Our model involved operating on the ewe during the third trimester under epidural anesthesia, putting electromagnetic flow probes on the uterine artery, the uterine vein, and the umbilical artery and vein, then cannulating a limb artery and vein in the fetus and cannulating a peripheral artery and vein in the mother, and then bringing all this out to a
pouch in the side of the mother. We could connect everything to a multichannel recorder, and then let the ewe recover for several days. Then we could hook the ewe up to the recorder and inject a drug and get real-time readings on fetal and maternal blood pressure, blood flow, uterine and systemic blood flow, and we could sample fetus and mother during the drug infusion.

It was a very ambitious project and took an enormous amount of work, but we did get a few studies out of it and did publish some work on it. I tried to select a variety of drugs. I used penicillin as a drug that would be actively transported. Interestingly, we found that the flux of penicillin from fetus to mother was greater than from mother to fetus.

DR. NEVILLE: Interesting.

DR. KAUFFMAN: Yes. There are surprises in research when you actually do it.

DR. NEVILLE: Otherwise, it wouldn’t be research, right?

DR. KAUFFMAN: It’s a polar compound, so passive diffusion didn’t play as much a role as the active transport.

Then we looked at the drug phenytoin because we wanted to study a highly protein-bound drug to look at the influence of maternal and fetal protein binding of a drug and what that did, if anything, to placental transfer. The way we did our experiments was that we infused the mother to steady state and held a steady state level so that we could look at the fetal and maternal concentrations at steady state, presumably steady state, and calculate the flux across the placenta in both directions. One of the surprises we found in the phenytoin study, looking at the impact of protein binding, was that, yes, the binding of phenytoin was significantly less in the fetus than the mother. But even when we adjusted in vitro experiments, when we adjusted the total albumin content in maternal and fetal serum, we still observed a difference in binding. So, what we thought we were seeing was not so much an effect of albumin concentration, but an actual difference between the fetal albumin and the maternal albumin in terms of affinity for the drug. So, that was another little bit of a surprise.

About that time, methadone was starting to be used widely as a drug for managing opiate dependence, particularly heroin dependence. There were mothers around the country who obviously were on methadone during pregnancy for that reason, and I decided that would be a good area to look
at.

I should back up. The other drug group I looked at was aminoglycoside antibiotics because I wanted to look at a drug that was distributed in total body water so we could see any fetal and maternal differences there.

I also decided to look at methadone, so we did that in the animal model, and pretty much saw what we thought we were going to see—that the highly lipid soluble drug distributed very rapidly and equalized between mother and fetus.

About that time, I had also realized that there were some significant differences between the ovine placenta (the sheep placenta) and the human placenta—real important anatomical differences, as well as possibly physiologic differences. I thought we really needed to see if we could devise some type of protocol for looking at this in humans. Not in the same way, obviously, but getting some information in humans. A colleague of mine in obstetrics at the time collaborated with me. We did a human study where we gave an aminoglycoside to a mother preoperatively, the excuse being this was part of her preoperative antibiotic regimen, and then sampled the mother and the baby at the time of delivery or surgical abortion. That was when we discovered there were significant differences in what we were seeing in the animal model and human model with the aminoglycosides.

We set up a protocol to look at methadone because we thought that was a real-world issue and would be clinically important, as well as investigationally interesting. But at that time, methadone was controlled by making it an investigational drug, even though it was being used widely clinically. So, we had to submit an IND [investigational new drug] exemption before we could do that study. It was approved by our local IRB, but we couldn’t do it until we had submitted an investigational new drug exemption, which we did. The FDA, when you submit an IND, as you know, has a finite period of time to deny permission to do the study. If they don’t contact you because of a safety issue or some concern, then you can go ahead with your research, your human study.

DR. NEVILLE: Ralph, I’m going to interrupt just for a second. In context, this was in the period of late 1970s, right? Mid-1970s?

DR. KAUFFMAN: It would have been in mid-1970s, right.

We were waiting until the review time was up for the FDA to go ahead and proceed. One day—I can remember this vividly—at 2 o’clock in the
afternoon, I got a call, out of the blue. I answered the phone in my office, and a voice said, “Hello, Dr. Kauffman, this is Dr. Frances [Oldham] Kelsey. I’m looking at your study here at the FDA, and you cannot do this. If you decide to proceed with it, we’re prepared to challenge all of the federal funding to your university.” And so, I didn’t do any more placental transfer research. [laughter] That was the end of my placental transfer research.

I knew of Dr. Kelsey from my time at the FDA. When I was there, she was a young medical officer who had become very famous for bringing the thalidomide application to everyone’s attention, which then precipitated the hearings that led to the 1962 Drug Amendments. I had been there when all this was taking place, so I knew who she was. She had moved on up into the higher echelons of the agency by the time I was a young faculty member. Anyhow, that brought an end to that area of research.

In the next iteration of our center grant, I decided I could study transfer into breast milk. I got funding the next time around for projects there. I pursued that, and that was quite doable. In my practice, I had a cadre of mothers who were very willing to participate. So, we did some work that way. But I lost interest in that after 3 or 4 years and decided the money really was in doing clinical studies in kids, looking at the impact of age and growth and development on drugs. At that time, pharmacokinetics was the big buzz tool. My work then shifted to doing clinical studies of different types of drugs to look at the effect of growth and development on the biodisposition of drugs. That was really the backdrop to what I did the rest of my career—the research aspect.

Obviously, I was aware of it, but that led me into a more intense awareness of the lack of such studies in kids and the need for them. That was coming to the fore with other people, particularly in the Committee on Drugs. I think that had an impact on my interest over the next 15 years as we pursued that agenda nationally.

DR. NEVILLE: The refusal to allow you to study the methadone sort of shifted everything.

DR. KAUFFMAN: It forced me to shift my focus. I mean, I would have liked to have continued. I think placental transfer of drugs is an important perinatal issue, but I don’t regret having shifted to the other because I think it actually ended up, in the long run, having a bigger impact on pediatric therapeutics than that initial work.

DR. NEVILLE: It strikes me that I think there’s going to be similar issues
with the study of marijuana in this day and age.

DR. KAUFFMAN: There very well may be, yes. Any time you touch on a highly politically, ethically charged area of research, it’s going to be difficult.

DR. NEVILLE: Let’s talk about, if you want, some of the pharmacokinetic studies you did then. I’m guessing HPLC [high performance liquid chromatography]. We talked a little bit yesterday about the technology in pharmacogenomics, and it would be interesting to hear your perspective on what technology there was to do analytics for pharmacokinetics.

DR. KAUFFMAN: Analytics was one of my biggest challenges because we certainly didn’t have the analytical capabilities or tools that are available today, or were even available 10 years ago.

I have to tell you one of the things, early things. We set up in our center assays of several drugs as a clinical service. Dan Azarnoff wanted to be able to measure digoxin for clinical monitoring. There was no standardized commercial method in the early 1970s to measure digoxin. There were different centers that developed immunoassays, but there was no standardized or commercially available method. So, to set up our digoxin assay—this is just an example of where we were in our lab—we had to grow our own antibodies in sheep, and then harvest and purify the antibodies on columns, and standardize them. We used tritium labeled digoxin then. It wasn’t a cold label assay. We had to grow and lyophilize our own antibodies, had to standardize the assay, get tritium labeled digoxin, and then laboriously do the assay each time. It was a real challenge, because once you grew a batch of antibodies, that antibody was unique to any other batch you grew later on. They all had to be restandardized. So, it was a very laborious process, but that was the way we initially did it. It was wonderful when eventually standardized fluorescent antibody techniques became available commercially.

DR. NEVILLE: I bet.

DR. KAUFFMAN: And much easier. We had gas chromatography [GC]. We had HPLC. We didn’t have the highly-automated machines then. A lot of our work was done with manual injection onto the columns, either HPLC or GC. A lot of my initial assays that I used were gas chromatography with flame detection. Those weren’t terribly sensitive. They were orders of magnitude less sensitive than what we have today, so sometimes we had to use a larger sample size. That became a challenge with pediatric studies, of course. Then we had HPLC. Then we eventually got some of the early models of the HPLC
and mass spectrometry detection. I really never had a chance to use that—certainly not during my fellowship. By the time it became generally available and applicable, at least at our center, I was into doing other things and depending on people in the lab to do those assays. I didn’t do them myself. But I did a lot of the HPLC and GC in the early phases. We used thin layer chromatography, which was difficult because it’s so semi quantitative and so susceptible to error. At least I thought it was. You could use 3-dimensional thin layer. In some of my earliest studies, in my studies of aminoglycoside and penicillin placental transfer studies, I used bioassays for the antibiotics.

We didn’t readily have easy computer technology to do our calculations. One of the first studies I did, we had to use a centralized main frame IBM computer. We put all of our raw data on punch cards, and then we took this stack of punch cards down and waited for our turn on the machine to run the punch cards through and get our output. I got in on the tail end of that technology. Of course, over the years, it morphed into programmable calculators, and then desktop computers, and then software developed that we could use to do that.

But early days of, for example, pharmacokinetic studies, a lot of that had to be done manually and graphically to do our PK [pharmacokinetic] calculations. It was only when the data processing tools became more readily available that we were able to do more sophisticated studies and more extensive studies, and do them more rapidly. Calculations were much easier, and the modeling became easier. It was much more accessible to everyone. I watched those tools develop through the years.

DR. NEVILLE: That’s amazing. The thought of having to calculate every subject’s AUC [area under the curve] by hand makes my head hurt.

DR. KAUFFMAN: Absolutely. You certainly learned the fundamentals of it, which I think a lot of the trainees now don’t. They plug their data into a black box and get this output. Having had to do that, I think I, and others of my generation and right behind me, understand the potential errors in the black box better than the people who put it in and take whatever’s spit out.

Anyhow, that’s a taste of what it was like during that time. The tools that developed during my fellowship and early faculty years were analytical tools. They really developed tremendously during those years and accelerated our ability to do studies in kids, and also the analytical tools. PK and PD [pharmacodynamic] calculations and data handling became much more accessible.
DR. NEVILLE: So, we’re in an era now where it’s, in some ways, easier to study smaller children because there’s less blood volume needed. At that time, with the technology, I’m imagining you needed a fair bit for each sample compared to half a mL [milliliter].

DR. KAUFFMAN: Compared to now, but we worked very hard to dial it down. Sometimes that elevated our limits of detection, but we worked very hard to get the volumes down to where they were realistic for younger children, and by and large, were successful. Some studies we just couldn’t do at the time because we couldn’t devise the analytical technique for it.

The other thing that developed from the mid-1980s into the 1990s was the molecular biology techniques that then came into more general use. That opened up a whole new area of being able to look at the genetics of drug metabolism. There was a lot of work done early on, from the 1960s forward, in drug metabolism. I don’t remember exactly, but probably the late 1960s and the 1970s, there was the realization that there were genetic differences, for example, in isoniazid and other substrates, that were really different among individuals, although we didn’t know the specific genetics of it. I remember going to a lecture during my fellowship. The title of the lecture was “Will the real P450 stand up?” At that time, they had defined 2, [cytochrome] P448 and [cytochrome] P450, because there are different light absorption characteristics. That was the prelude to then discovering that there were thousands of P450s and genetic control of their expression and so forth.

DR. NEVILLE: That’s amazing. Is there anything else you want to comment on during your time at KU [University of Kansas]? Because I also want to get into what led you to Wayne State and where you were with your funding and science.

DR. KAUFFMAN: As I said, my major limitation at University of Kansas was that it was a smaller pediatrics department, so I didn’t have the patient population I felt I needed to be able to enroll into studies.

About that time, I came to know Sandy Cohen, Sanford Cohen, who had become chairman of pediatrics at Wayne State University, at Children’s Hospital of Michigan. We had served together on the [AAP] Committee on Drugs and came to know each other. I think we’d actually co-edited an issue of Pediatric Clinics North America by then, too. So, we knew each other. Sandy became chair at Wayne State and contacted me. He was very interested in promoting clinical pharmacology, and as a new chair, used that as an opportunity to set up a unit at Children’s Hospital of Michigan in Detroit. He contacted me and asked me if I was interested in moving. It was a
time where I was becoming increasingly torn between clinical care, administrative demands, research, and what I was going to do now in the next step. I was a tenured associate professor, but I sort of felt like I was at a blind end at that point. It was an opportunity for me, and so I decided to move to Wayne State. The advantages for me were that there was a pediatric clinical pharmacology unit he had set up that was a couple years old and also there was a large patient population and administrative support for this activity. It ended up being a very good career move for me. That was sort of, in a nutshell, the story of my move to Wayne State in 1979.

DR. NEVILLE: So, that was about 10 years from when you had become an instructor at the University of Kansas. I’m interested, if you can recall, in that 10 years. We talked yesterday about Sumner Yaffe and that there were various scattered people across the country working on peds clin pharm [pediatric clinical pharmacology], but not really as a discipline. You were likely the first peds clin pharm fellow on a training grant. In that 10 years, before you moved to Wayne State, had you seen the field evolve at all, and if so, how?

DR. KAUFFMAN: Oh, yes, it was evolving by fits and starts. One of the problems was that there was still a lot of controversy about the ethics of including children in research. The other major handicap was that the pharmaceutical industry had absolutely zero interest in studying new drugs in children. The FDA took pretty much the same tack. They took a rather passive tack to this issue and said, “We can’t force companies to do studies they don’t want to do.” The companies had multiple excuses for not studying new drugs in children. What was happening during that time was that there was an explosion of drug development and drug studies in adults, and a whole infrastructure had developed across the United States in a number of major centers to do clinical pharmacology in the adult population. But this was not happening in pediatrics. Increasingly we were seeing a number of people around the country saying that this was wrong. We needed to find a way to bring clinical pharmacology to children so that drugs could be developed in children for appropriate dosing and to understand their safety in children and the differences—the different ages of development, how drugs are handled, responses to drugs, and so forth. The Committee on Drugs of the Academy was sort of leading the charge on this at the time, too. But it was a real uphill struggle because there really wasn’t at the time a political will in the federal government to do this, certainly not at the FDA. There was a reticence, even on the part of the Academy outside the Committee on Drugs, to really support this. There wasn’t opposition to it. It just wasn’t a priority at that point.

There were a handful of us saying this. Harry Shirkey was one of the leaders
saying that kids are being deprived of new drugs, they need to be included. Sumner was an advocate of that. There were a number of other people. John [T.] Wilson wrote several papers about this, and others did too, trying to bring this to attention. That was starting to foment, but the political stars hadn’t lined up yet in the 1970s and 1980s to really make this happen. But it was coming forward. The Committee on Drugs had written the original ethical guidelines, had written a booklet on the issues around how to do clinical trials in children. There started to be some advocacy within the agency [FDA]. The Committee on Drugs by then had, in the early 1980s, a contract with the FDA and was starting to get some support there. It was starting to move, but very slowly at that time.

DR. NEVILLE: How was funding? If everyone was sort of reticent to study drugs in children, were you able to continue to get funding?

DR. KAUFFMAN: It was very difficult. We were able to get funding for certain classes of drugs. The industry had an incentive to fund vaccine studies because there was a significant market in children for vaccines and many of the new antibiotics they were studying. So, in terms of clinical studies, industry-funded studies, we could get funding for some of those, and occasionally other drugs. I remember I got a little bit of funding from Ciba [now Novartis after several mergers in 1996] at one time to study methylphenidate. So, there were sporadic things, but in terms of being able to get funding for the pipeline of drugs to do studies in children, as well as adults, it was really very difficult.

DR. NEVILLE: And, I would imagine, somewhat frustrating.

DR. KAUFFMAN: Funding from the NIH, once I was out from under the umbrella of the center, became much more difficult, too, until the PPRU [Pediatric Pharmacology Research Unit] was finally funded in the early 1990s.

DR. NEVILLE: I don’t want to forget to talk about that.

Before we go on to detail of Wayne State, in our past session, you said one of the greatest things you learned from both your mentor at KU and the FDA was the ability to write scientifically. What else would you say are the largest or most impactful things you gained from your time at KU?

DR. KAUFFMAN: Several things. One thing that comes to mind is that, when I was finishing my fellowship, there were very few positions around the country in academic pediatric departments for clinical pharmacologists. It
wasn’t a priority for most departments. But I got calls from several people, and one of those calls was from Dr. Shirkey, who was then chair at Tulane. He wanted me to come down and interview there, which I did. I ended up not going there. But, interestingly, a couple years later, when I was a young junior faculty at KU, Dr. Shirkey came out and did a 1-year sabbatical with us in our unit. So, I had the opportunity to spend a year around him just learning to know him better as a person. He gave me a lot of insights into the history of pediatric therapeutics and his philosophy about things. He was the reason I ended up on the Committee on Drugs because he was one of the founding members. While he was on this sabbatical, he said, “Ralph, you should be on the Committee on Drugs,” and he made it happen. I was only probably out of my fellowship 3 or 4 years when I went on the committee. I was very junior, but I ended up serving on the committee, either as a liaison, a member, or a consultant for the next 18 years. The last 3 or 4 years I was chair of the committee. It was one of the opportunities that wouldn’t have happened for me if I hadn’t had the privilege of knowing Dr. Shirkey. Of course, being able to visit with him off and on for a year, I learned a lot of the ins and outs of how he thought and what was behind his editorial in 1968 calling everyone’s attention to the fact that children were therapeutic orphans.

The other influential person, in addition to Dan Azarnoff, who really encouraged me, was the then-chair of pediatrics, Herb [Herbert C.] Miller. Herb Miller came to University of Kansas from Yale as a newly minted pediatric neonatologist in his early 30s, which was very unusual back in those days. He had an intense interest in human development, particularly neonatal development, and did a lot of publishing in his early career in that area. He was one of the people who really encouraged me to go into academic medicine. He made sure that I had protected time the first 5 years. He gave me a new laboratory, made sure I had internal, as well as external funding, and really mentored me into the arena of academic medicine. That was tremendously important, too. He didn’t really have a primary interest in pharmacology, but he understood the importance of it and how it would relate to clinical pediatrics and was very supportive. He was another person who was very influential.

DR. NEVILLE: I want to talk a little bit as a segue to your time at Wayne State. We talked yesterday how you never learned to balance research and clinical and administrative. You just learned to realize that you will never balance it. You talked about having to make some choices in your recruitment to Wayne State, give up some of the clinical. Let’s talk about what your job looked like and how that was for you.
DR. KAUFFMAN: I was at Wayne State University School of Medicine, Children’s Hospital of Michigan for 16 years, and my job, of course, changed during the years from time to time. One of the things that changed immediately when I made that move was that I decided I couldn’t do what I needed to do in the laboratory in clinical studies and also do outpatient medicine, because outpatient pediatrics can be very consuming. So, I gave up outpatient pediatrics at that point. I decided I needed to focus more. I served as attending during most of those years for anywhere from 4 to 6 months a year because I enjoyed clinical medicine and I enjoyed teaching. The last few years I was at Wayne State in the mid-1990s, I cut my inpatient attending to 2 months a year. But up until then, for 3 or 4 years, I was vice chair for clinical services at the hospital, so I was not only supervising some hospitalists, but I was also attending 6 months out of the year, inpatient.

DR. NEVILLE: And doing research.

DR. KAUFFMAN: And trying to run a laboratory and some clinical trials. I was trying to do—

DR. NEVILLE: Clearly balanced. [Laughs]

DR. KAUFFMAN: I wasn’t very balanced. I eventually, as that went on, gradually cut down my clinical inpatient work. But I always had this tremendous tension between wanting to be a clinician, but not wanting to give up the research, or vice versa. So, I fought it until the last 10 years of my career, and then I finally said I can’t do all of this, especially when I moved to back to Children’s Mercy in Kansas City and was supposed to set up a new research entity. I really had to focus on that, so I really cut back my clinical work tremendously, and I missed it.

DR. NEVILLE: Let’s talk about that pull a little bit, because I think that’s something that’s not talked about a lot, but common. I know I experience it.

DR. KAUFFMAN: Everybody experiences it. One thing this did for me was that it gave me a lot of insight later on when I was talking to young faculty because I could empathize with what they were going through and try to communicate to them how to think through that. It’s a personal choice and a personal decision for everyone. But I think it must be a tension for everyone who’s trying to be a triple threat. There’s always this tension. Some people do it much better than others.

DR. NEVILLE: I think we’re at a time where work and family balance is emphasized and important. How did you, or how do you, feel about your work
and family balance, and how did you do that?

**DR. KAUFFMAN:** I’m sure I didn’t do it as well as I should have, but I tried to be as much a part of my kids’ life as they were growing up as I could, but I couldn’t be as much as I probably would have liked to. But I did take time in the evenings, usually, to spend some time with them. I tried to get to all the soccer games and baseball games and school activities, and go watch the marching band at the Friday night football games, and be as much a part of it as I possibly could. We took family vacations. I made sure we had family vacations a couple times a year so we could get away. I tried to carve out time, and then there were times when I just wasn’t available on weekends if I was on call or something. I think my family understood. Although I’m not sure, because neither of my kids wanted to have anything to do with medicine. I don’t know if that was a reason or not. [Laughter]

**DR. NEVILLE:** When you went to Wayne State, did you continue with pharmacokinetics? Let’s talk a little bit about your research and the directions you ended up going and how.

**DR. KAUFFMAN:** All my work at Wayne State had to do with some aspect of clinical trials and PK studies. Some of those publications have to do with development of assay methods, because we were constantly trying to develop either assay methods for a new study or refine assay methods. Fortunately, I had people, good laboratory people to work with to do a lot of that hand work, to do the actual work. The focus there was really on clinical studies, PK, and analytical development. I think most of what I published during those years reflects that in some way. I did get involved in the ethics aspects of it, too, because that was unavoidable. I ended up writing a little bit about that and giving talks about it. A lot of my time was spent, too, at that point, working on the Committee on Drugs, committee affairs, and getting involved in some of the political aspects that were starting to come forward. And also, at the end, NIH.

**DR. NEVILLE:** That’s a good segue. We may bounce around a little bit, but I would like to talk about some of your national work. So, let’s start off with the Academy. Before the Committee on Drugs, had you been involved, or did you get involved because of the committee? What was your involvement with AAP?

**DR. KAUFFMAN:** You mean being on the committee or serving with the committee?

**DR. NEVILLE:** Yes. So, I sort of fell into the AAP because of the committee. I had been an AAP member.
DR. KAUFFMAN: Yes, that was the gate for my real engagement with the Academy. I was a member, of course, once I finished my residency. At some point shortly thereafter, I joined AAP, probably around the time that I got my boards. Other than going to meetings, I hadn’t really participated. I was involved through the years off and on with section leadership, too. The Committee on Drugs was really the significant entree into being involved with the Academy and working with the Academy during those years. It was a very beneficial thing for me to be a part of that, especially during that period of history when we were trying to get [United States] Congress’ attention and get institutionalized changes to the food and drug laws to benefit children.

DR. NEVILLE: So, let’s talk about that. Were you going to Washington? How did that unfold back then?

DR. KAUFFMAN: It unfolded over time. The earlier parts were working primarily with the FDA. Early, I think it was already in the late 1970s, we were asked under a contract to develop a list of essential drugs that needed to be studied in children. I think I still have that packed away somewhere. Nobody else has it because nothing was ever done with it. We developed this extensive document of essential drugs that needed to be studied in children in the late 1970’s under that contract.

DR. NEVILLE: I would love to see that if you do have it.

DR. KAUFFMAN: I don’t know if I still have it or not. That essentially went nowhere. But probably the most important things we did during those years was developing some of the statements to guide pediatricians. We developed statements on a variety of things, but probably the most important ones, vis-a-vis therapeutics, were the guidelines for studies in children in 1974, the ethical guidelines in 1977, and then, subsequently, updates of those, because they had an impact. One of the biggest arguments against including kids was the ethical argument. Although it was a straw man much of the time, the real elephant in the room was the economics of it, but nobody wanted to admit that. The arguments were frequently framed around the ethical concerns. We tried to deal with it by publishing these guidances, and that influenced, of course, the federal policies. But we couldn’t get legislation moving, and there were multiple attempts to do that.

I think one of the things that really broke the dam was in the early 1990s. I don’t know if it was 1991 or 1992. Finally, Duane Alexander at NICHD [Eunice Kennedy Shriver National Institute of Child Health and Human
Development], the FDA commissioner, PMAF Pharmaceutical Manufacturers Association, and the Academy of Pediatrics all sponsored a three-day workshop in Washington, DC to look at the impediments to doing drug studies in children. This was very early 1990s—1991, 1992. Out of that came a report. I can’t tell you all of the recommendations without looking at it, but the essence of the report was that Congress needed to step up and pass legislation that would facilitate pediatric studies; the pharmaceutical industry needed to knock down impediments, from their perspective, to doing studies; the NIH needed to look at funding for pediatric studies, increase funding for pediatric studies; and so forth. Over the next 5 years, every one of those recommendations was, in some way, addressed.

In the early 1990s, I was chair of the Committee on Drugs. After that meeting, it must have been in the early 1990s, about 1994 or along in there, at the fall Academy meetings, David [A.] Kessler, then commissioner of the FDA, and I shared a podium on a plenary session. I gave a general talk—the sermon about needing to do drug studies in children, this was why, and what hasn’t been done, and so forth. Kessler followed me, and then announced what the FDA was going to do initially and what they could do without new legislation to push this along. Because Kessler was a pediatrician, he was always very supportive of this during his administration at the FDA. That started breaking the dam.

From that point forward, then, the Academy—the Washington office, as well as the Chicago office, but the Washington office really led the way then—started a strong advocacy effort over the next few years for getting legislation passed that would do this. It’s a whole new story that, over a period of probably the next 8 to 10 years, several legislative changes were passed by Congress, amendments to the Food, Drug and Cosmetic Act of 1938 that created an economic incentive for pharmaceutical companies to do pediatric studies and created a whole new infrastructure around the country for pediatric pharmacology.

**EXPLANATORY NOTES ON LEGISLATION:** The FDA Modernization Act of 1997, provided that in return for the voluntary completion of studies specified by the FDA in a Written Request (WR), the sponsor of the drug would receive a 6-month extension of market exclusivity resulting in protection from a competitor marketing a product with the same active ingredient. Market protection applied to all products that contained the active moiety and essentially extended the market life of the product.

A Final Rule promulgated by the FDA in 1998 required study of new drugs in the pediatric population that might provide a therapeutic benefit to pediatric subjects
and that might be used in a substantial number of pediatric patients. However, this rule was struck down in a court ruling by Judge Henry Kennedy, Jr in 2002.

The provisions in the “1998 Final Rule” were codified in the Pediatric Research Equity Act (PREA) of 2003.

The next iteration of FDAMA, titled the Best Pharmaceuticals for Children Act (BPCA), which passed in 2002, preserved the voluntary incentive program to extend market exclusivity. Both the BPCA incentives and the PREA requirements were made permanent in 2012.

There was a lot of effort in terms of advocacy at the congressional level. The Washington office led the charge. They were a tremendous help. In addition to me, I remember Jeff Blumer, Phil Walson, Greg Kearns, Bob Ward. All the names in pediatric pharmacology that you can think of, at various times, were up on the Hill meeting with congresspeople and advocating for this. We took turns-testifying on the specific legislation at hearings from time to time. I participated in several of those during those years.

The opposition was interesting as we tried to get this legislation through, different pieces of legislation, and then renewals at 5-year intervals. It was an interesting coalition. We were opposed initially by the generic industry because they felt that this would give pharmaceutical companies a mechanism to prolong their patent protection, and thereby delay the generic access to products. So, they opposed it. Interestingly, then-Senator Clinton from New York opposed it because she thought it would be a windfall for the pharmaceutical industry. She was one of our hardest nuts to crack. We had political conservatives in opposition. We had political liberals in opposition for different reasons. It was a real political education for me to watch the Washington office maneuver with all the different entities—congressional entities and their staff—to try to bring this to fruition. It was a wonderful thing to see once the initial legislation came through to provide economic incentives for pharmaceutical companies and also some other requirements for them to actually do the studies—sort of a carrot-and-stick approach. Congress was very concerned about this, whether it would really work. It worked immensely well.

DR. NEVILLE: Ralph, at that time, as the legislation was coming down, but before it was implemented, were the drug companies on board or not in favor—aside from the generics?

DR. KAUFFMAN: In general, I think publicly they were opposed, officially
and publicly. They were very concerned about this. Their arguments centered around legal liability issues that they were concerned about and ethical issues. But it was interesting that once the legislation went through and there was a strong financial incentive to do the studies, all the ethical and legal arguments evaporated.

DR. NEVILLE: Very quickly. [laughter]

DR. KAUFFMAN: Rather quickly, yes. So, they were publicly opposed. But I should say that, particularly in several of the large pharmaceutical firms, there were individuals in leadership positions in those firms who were very supportive of this. Les [Lester F.] Soyka was a pediatric cardiologist who was at—I forgot which company he was with [Bristol-Meyers Squibb Company]. He’d been in academic medicine for a long time, and then was with one of the large pharmaceutical companies. He was very supportive and gave us a lot of good advice when we were working toward the legislation.

Marion [J.] Finkel, who was at Sandoz [Pharmaceuticals — now a division of Novartis] at the time, was very supportive and very helpful, particularly behind the scenes in advising us in what would work and what wouldn’t work—very supportive. And there were many others.

Later on, when Steve [Steven P.] Spielberg, who left academic pediatrics and went with Merck [and Co., Inc.], and then with J&J [Johnson & Johnson], of course, was tremendously helpful in supporting this during the period of time he was with those 2 large companies.

There were individuals both at the FDA and in the industry who were very supportive and gave a lot of help in getting this done. But publicly, at the corporate level, they were opposed, yes. In fact, when the Pediatric Pharmacology Research [Unit] network was initially founded for the first 2 years, we thought that if we created an infrastructure to do these studies, industry would be anxious to use this. They stayed away in droves. We could not bring any significant industry studies into the PPRU until this legislation took effect and they had a way to fund it and saw they were going to have to do it. At that point, then the studies started coming in.

DR. NEVILLE: I’m trying to remember what year the PPRU started.

DR. KAUFFMAN: You’ll have to check this, but I think the initial funding year was 1994.

DR. NEVILLE: That was probably a result of all the initiatives that said,
“Hey, NIH, you need to start funding things for children.”

**DR. KAUFFMAN:** That was a part, yes. Sumner Yaffe really led the charge at the NIH for that. He had a deep and strong commitment to making this happen. And Duane Alexander, who was head of NICHD, was extremely supportive, too. They were the ones who took and carried the banner at the NIH. There were people at the FDA who led the charge at that agency. The Academy was working over several years with various congressional staff to get key congresspeople and senators to sponsor the legislation, and finally got the 2003 PREA bill to a vote.

**DR. NEVILLE:** But you didn’t know for sure if it would pass.

**DR. KAUFFMAN:** Oh, it was up in the air. It was initially passed with a 5-year sunset, and so as the 5 years came up, we had no assurance that it would be renewed, but it was. Then later on, in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) legislation, BPCA and PREA were made permanent. So, it’s now the law of the land. The people now, who came in after the fact, just assume it’s always been there.

**DR. NEVILLE:** Exactly, which is one of the points I wanted to have you expand on, because I remember, I think it was, the second sunset. It was quite nerve-wracking because you had made all this progress and you didn’t know if it would stay. So, can you comment on what that was like and how you felt? Because I think you’re right, people now think this is how it always was.

**DR. KAUFFMAN:** Well, this is a complex story, because there were several pieces of legislation that interacted to provide the economic incentive for companies, but separate legislation, initially, that provided a requirement that certain drugs be studied in kids.

The first law passed was the 1997 FDA Modernization Act that provided economic incentives to do pediatric studies. Then in 1998 the FDA had, by regulations based on existing food and drug law, tried to regulatorily mandate studies on certain new drugs for kids. That was challenged in court before the 5 years was up. That was challenged in court in the state of New York, and actually the court negated that regulation. So, there was about a 2-year gap where that regulation was null and void by court order, so we were in limbo. The companies continued to do studies that could qualify for the extended exclusivity, but they weren’t required during that time. The FDA couldn’t enforce their regulation to require them to do studies under certain circumstances. One of the efforts we really worked hard on was to get that requirement piece in the next iteration of the FDA food and drug law
amendments, and that was up in the air. That 2-year period was why everyone, including the companies, were in limbo because they didn’t know if the requirement to do pediatrics studies was going to be legislated. There was a lot of opposition to it. I don’t think it would even have a chance to be brought up for a vote now. It probably wouldn’t even get out of committee today, in today’s Congress. The timing was very critical.

DR. NEVILLE: That was the first sunset, right?

DR. KAUFFMAN: That was the first sunset. I may have my dates wrong, but FDAMA was initially passed in 1997, then Congress renewed it as BPCA in 2002. I can’t remember for sure.

DR. NEVILLE: I can check the dates.

DR. KAUFFMAN: But then Congress finally passed the PREA in 2003 that codified the regulation that had been negated by court order. So, then we knew that we had both pieces. We had the requirement to do studies in children and we had the economic incentive for the companies to do it. They were a little different in what drugs they applied to or what kinds of studies from time to time, but they had a profound effect on the number of studies that were done and the variety of therapeutic categories that were included that had never been included for children before.

DR. NEVILLE: You made a comment that’s interesting to me that, if you can, I’d like you to expand on. You made the comment that you don’t know if it would get out of committee today. I’m trying to remember; do you think it was because it was Democratic or because people worked across the aisle better? You were dead center in it, right, working very closely with the Washington office? Can you comment on the political landscape and maybe how it’s different today, and why? You said the timing was critical. Why?

DR. KAUFFMAN: You’re going to get me in trouble here. [Laughter]

DR. NEVILLE: No I won’t. We can edit it out if it’s too controversial. But I think it’s an important history.

DR. KAUFFMAN: I think there really is a difference here. We’re talking about the period of about 1995 to 2010 where all this transpired, until the legislation finally became permanent. I think in the time that we were doing the advocating for the initial legislation, and also the 5-year renewals, I think there were significant political differences and divides in Congress. But they were working together so that you could work with their staff and with the
congresspeople and senators. You could develop coalitions of interest where you could develop a will to do the right thing across a political spectrum. As I said, the opposition at certain points wasn’t necessarily Democrat/Republican or conservative/liberal. It was that they might oppose the legislation for totally different reasons, but they both had to be convinced that it was okay.

On what you might call the conservative side, there was a major concern that this would impose unnecessary regulation on the pharmaceutical industry. It might impede the availability of drugs for adults, or delay them for adults. That it would impede research for adult medications. And some people, just frankly, didn’t think that it was necessary. Children weren’t a priority. But that was a small minority.

On what you might call the more liberal wing of Congress, the concern was that this would create a windfall for the industry, and that wasn’t fair. Or, it would delay the availability of generics to the adult population and raise the cost of medications.

Those were all concerns on both sides of the aisle. The challenge was to work with those parties to try to develop legislation that would be workable for them from their different viewpoints. The difference, I think, between then and today is that then they were willing to work toward a center. Today, there’s no willingness, generally, to work toward a center. So, I don’t think we would be able to get that kind of coalition today, in today’s Congress, to get that done. That’s just reality. It’s not a political position, it’s just reality. So, I think we’re fortunate that the stars lined up during that decade so we were able to get this done. Children are very fortunate that the stars lined up.

DR. NEVILLE: You were there when the sunset rule was removed, right? I think it’s viewed as a huge win for children and the Academy. Can you comment on that? Now it’s FDAAA [Food and Drug Administration Amendments Act of 2007] and FDASAIA [Food and Drug Administration Safety and Innovation Act of 2012], and BPCA [Best Pharmaceutical for Children Act of 2002] and PREA [Pediatric Research Equity Act of 2003], and the stuff we know today. I think there’s always some fear that sunset could come back, but it would be a lot more difficult.

DR. KAUFFMAN: I don’t think that. There’s no statutory reason that the sunset would occur. It would take an act of Congress to change the food and drug law at this point. So, I don’t think it’s a big threat.

But back to what I thought you were saying. It was really a big, big deal.
when PREA was finally passed in 2003. As you know, I was at Children’s Mercy hospital in Kansas City when this happened. Our clinical pharmacology unit there was very active and one of the pediatric pharmacology leaders. Greg Kearns and others were very active in advocating for this legislation. I had been working with the Washington office on this, too. After the 2003 PREA was passed, the Washington office sent me a framed copy of the legislation with President [George W.] Bush’s signature at the bottom, and I thought, that is really neat. I thought it was particularly good that a president who identified as a political conservative signed this legislation for kids. I think that’s important. It showed a willingness to do the right thing.

DR. NEVILLE: And the culmination of 20 years, at least.

DR. KAUFFMAN: The culmination of 20 years of advocacy and work to get this done.

DR. NEVILLE: Ralph, I’d like to shift gears a little bit and talk about the PPRU, since you were so involved. We talked a little bit about its beginnings, and I think it’s made some key contributions for children. Now there are subsequent funding mechanisms, but I was one of the first PPRU fellows, so it’s near and dear to my heart. For people who weren’t around, can you describe what it was like? To my knowledge, it was the first organized consortium/network around children in pharmacology.

DR. KAUFFMAN: Specifically pharmacology. There were a lot of networks funded by NIH, various institutes prior that had to do with children’s diseases.

DR. NEVILLE: Right, like oncology.


DR. NEVILLE: But nothing for pharmacology.

DR. KAUFFMAN: But there was nothing for pharmacology. To back up a little bit, in 1972, Dan Azarnoff sent me to a meeting at the NIH. I found the record of this a while back. The topic was to talk about the need for funding for pediatric pharmacology. It was held by NIGMS, [NIH] National Institute of General Medical Sciences. Interestingly, I was the sole pediatrician at this meeting. It was a small working group. I distinctly remember sitting at the table and being told by one of the internists that if the pediatricians would ever submit a competitive grant, it would get funded. [Laughter] It made me
so angry, and I think that’s why I remember it. But that was 20-some years before we really got things going. The problem was, we didn’t have people trained, we didn’t have any infrastructure to do this kind of work, and there was really no funding to do it. So, the conversation continued over the next 20 years. But the conversation that led, eventually, to the PPRU started in the early 1990s, from at least my experience with it.

I think we were all batting around, informally, the idea of how we could create funding for this and how we could create a critical mass [of investigators], because we didn’t have a critical mass at any single institution. There was 1 person, or 2 at the most, at any given place, except for maybe Toronto and Detroit and 1 or 2 other places. But there was no critical mass anywhere and no funding. So, we were batting this around—how can we do this? I remember conversations again with Les Soyka and industry about this after a 1991 conference in Washington, DC, and with the people at Sandoz and others in industry, as well as the NIH and the FDA. Finally, through those conversations, the idea gelled to try to set up from the legislative perspective this extension of patent protection for the industry in order to give them a financial incentive and for the NIH to create a network to do this.

In about 1993, Sumner Yaffe, who was at NICHD, was already working it. Sumner was leading the charge there at NICHD to try to set up a funded group and get the funding put together to do that. They got it forward to their council, and Sumner asked me to come and present the whole idea to their council about why it was important to do, which I did. There was a quiet response from the NICHD council—courteous, but quiet. Nobody was clapping their hands or yelling hurray. [laughter] They approved the funding for the PPRU network then. In 1994, when the request for proposals went out, we all applied. In 1994, they funded the first—I think it was 7 initially—PPRU sites, pediatric pharmacology network sites. Then, over the next year, some more were added on. Eventually, by the time that program was renewed several times, at 5-year renewals, I think we were up to 13 sites, finally, at the last iteration of it.

That was a very productive network, but one of the major mandates for the NICHD was to fund and provide an infrastructure that was available to industry to do this kind of work, something that wasn’t available at that point in time. Even if industry wanted to do pediatric studies—and they were being mandated and rewarded for doing it—they didn’t have the infrastructure to do it. So, this was NICHD’s approach to try to create part of this infrastructure. As the PPRU went on, the infrastructure around the country developed in response to the demand and the funding from industry, and the NICHD mandate sort of went away. It became less important for the
PPRU. The NICHD saw the importance of the PPRU morphing into more a scientific study group that could address more fundamental issues around developmental pharmacology. I’m not familiar with what happened within the NICHD, but at some point later on down the line, the decision was made to change the focus of the funding, to redo it with a different focus. Then the PPRU was replaced with other sources of funding.

But that 15 years of the PPRU was extremely productive and helpful and did something that couldn’t have happened any other way. So, we all owe a great deal of gratitude to Sumner Yaffe and Duane Alexander and others at NICHD for making this happen.

DR. NEVILLE: Clarify this for me. It sounds to me, from what you’re saying, that a positive unintended consequence was that you had all these sites that were gaining expertise, that each site was starting to have the infrastructure, so the ability to do pediatric pharmacology clinical trials was spreading across the country.

DR. KAUFFMAN: A lot of people responded to this demand—some who shouldn’t be in the business, some who did it extremely well, and a lot in between. One of the real shortcomings, and is still such, is that we don’t have adequate training sites to train people formally for pediatric pharmacology. There’s a constant struggle to get funding for that. Some of the T32 [Predoctoral Training Grants] money is providing that kind of funding. There are individual training grants at various sites that are doing it. Also, there’s been an effort on the part of NICHD in the last 5 years or so to extend pediatric training into funded adult training sites, too, and to increase the connectedness through teleconferences and so forth between training sites to enhance the training. So, it is happening, just not fast enough or involving enough people.

DR. NEVILLE: Do you think that’s because it is pediatrics, or why do you think that is?

DR. KAUFFMAN: I think one issue is that research and training money is very constrained now because of federal funding. So, there is less money to go around. There’s greater competition for the existing dollars than there probably was 10, 15 years ago, particularly for training. Another thing is that there’s competition between this kind of training, which is very research-based, and funding of training for clinical fellowships and resources for that at medical centers and training sites. Every medical school and teaching hospital has to set their priorities. Research is competing with all the other priorities for clinical training, and that’s a constantly changing environment
and challenge for training sites. So, unless the training funding is targeted for research, it’s hard.

The other thing that I think enters into this mix is that clinical pharmacology is a discipline that is different from most of the other medical clinical disciplines. Most, if not all, of our clinical disciplines are either disease or organ-based. Clinical pharmacology is neither. So, it’s had a hard time developing a solid identity. The other thing that exists, and has from the beginning, is that the discipline of clinical pharmacology can be entered from multiple routes, whereas for a pediatric endocrinologist or oncologist, there’s a set training sequence that leads to that certification. In clinical pharmacology, you can develop that expertise and be a member of the discipline from a medical background, from a pharmacist background, from a PhD background. People who are PhDs are doing clinical pharmacology. Pharmacists certainly are. They’ve been among the leaders in clinical pharmacology, as well as pediatric pharmacology, and then medical. They all come from a different training program. So, identity of the discipline has been a continuing problem through the decades, and still is. I think, in terms of getting funding, that enters into the gestalt also.

DR. NEVILLE: Which is interesting, because I think it’s one of the strengths of the discipline, too, right?

DR. KAUFFMAN: I think so, too. As I’ve watched the discipline develop over the years, I think the people who have the most to offer are the physicians who do their general specialty—pediatrics, medicine, psychiatry, whatever their general background is going to be in medicine—and then do a combined fellowship in a clinical subspecialty, plus clinical pharmacology. This combines all of the clinical and research expertise and pharmacologic expertise they’re going to need to really contribute. That doesn’t take away from the person who does it differently, but I think that provides the strongest training background for a person to contribute at this point. That’s my bias.

DR. NEVILLE: It’s been very successful, as we both know, in Kansas City.

Do you want to talk a little bit about your tenure in Kansas City? I know you’ve done a lot of mentoring and the PPRU went there because of you. It became a very, I think, rich time in the history of the institution for pediatric clinical pharmacology, and I would love to hear your thoughts on that.

DR. KAUFFMAN: Yes, I can talk a little bit about that. As you mentioned, in the first round of funding for the PPRU, I was at Wayne State, and we
were one of the first funded sites at that institution. Then, 2 years after we were funded there, I was recruited to Children’s Mercy hospital in Kansas City and was able to move the grant to that site.

DR. NEVILLE: Was it time to go back to your roots, or how did that recruitment unfold? Who recruited you?

DR. KAUFFMAN: I had no intention of moving anywhere.

DR. NEVILLE: [Laughs] Another twist.

DR. KAUFFMAN: It really was a twist. This is a story about a few very forward-looking people at Children’s Mercy Kansas City. There were multiple people involved, but the 3 people I recall who really had a significant role in this were Bob Hall, Robert [T.] Hall, who was head of neonatology at the time in the 1990s; Bill [William E.] Truog, who is still there in neonatology; and Brad [Bradley A.] Warady, who is still there, I think as head of [pediatric] nephrology. At that time, Children’s Mercy had very little research infrastructure or activity. They had a few individual clinical trials that people did from time to time under pharmaceutical clinical trials, but very little other research going on, and no real laboratory research base or organized research program. They, in their strategic plan, had decided they wanted to build a children’s hospital-based research program that would be competitive.

I wasn’t there then, but they spent several years studying what should be the central thrust or the focus or emphasis of this research entity they wanted to build. To my surprise, none of them being pharmacologists, they decided that clinical pharmacology should be where they were going to go with this new research entity. As a part of the strategic planning, they invited me, along with others, as consultants to come in and review their plan and talk to them about it. They were trying to decide whether this was a good idea or a blind canyon and a bad idea? Was this something that was going to go anywhere, or not, because they were planning on investing lots and lots of money in doing this. So, I went out as a consultant and subsequently was recruited to move back there and become the chair of their newly minted medical research department. It was not an easy decision for me because I was very secure in a tenured position where I was, and this would be a major change relatively late in my career. But it was a major, wonderful, new challenge, too, and I have never regretted for a minute that I did it. It, again, was a good move for me professionally, as well as personally.

So in 1995, I moved back to Kansas City, and then was fortunate to recruit
some very key people. Greg Kearns joined us 6 months after I arrived as chief of clinical pharmacology. He moved from University of Arkansas Children’s Hospital. Steve [J. Steven] Leeder, who was in Toronto, and 2 of his associates, who are laboratory pharmacogeneticists, moved a little later, about a year after I arrived. That was the nidus, and from there, we had the PPRU grant.

DR. NEVILLE: Which came with you, right?

DR. KAUFFMAN: Which came with me. Then, through Greg’s leadership and Steve Leeder’s efforts, additional funding came in subsequently in addition to the PPRU. That unit grew over the next 10 to 12 years into one of the leading units in the PPRU, and has continued to grow into one of the leading clinical pediatric pharmacology units in the country, in North America. That has been a source of great satisfaction to me. Others did the major work in making that happen, but I had the opportunity to get it started, and then I had to move a lot of attention into other research areas. But that was my entree into fundraising and developing endowed professorships and building new laboratory space and things like that. That was a fun thing to do, also.

DR. NEVILLE: But it has to be satisfying. I’m sitting here and I’m struck by how when you were training at KU, there was hardly anyone else, and now the place where you directed medical research is considered to have one of the leading pediatric clinical pharmacology training programs. It’s full circle almost.

DR. KAUFFMAN: I can’t take credit for a lot of that, but it’s extremely satisfying to see that having taken place, because the world has really changed tremendously.

DR. NEVILLE: You tried to retire once on us, when I was also there, and got pulled back in. We’ve talked a lot about your early experiences. Now, with all you’ve seen, with the legislation, your experiences, and then mentoring junior faculty and fellows, I’d be interested to hear your perspective on how the discipline has shifted, maybe even what you see for the future. In the context of yesterday, we talked about limited work hours, how we’re in the Information Age, the pressures on medical curriculum. How pharmacology is being trimmed, and how the art of prescribing is changing—all that. To start with, you can comment on your mentoring experiences and how that’s been and how maybe you see the trainees as similar or different from when you were training.

DR. KAUFFMAN: Well, the environment for the training was very different from mine, but there were other places around the country where there were
tremendous differences in training across institutions, too. So, I don’t know that I can really comment. A lot of the differences that might exist might be both across institution, as well as across time. But one of the big differences is that there are formal training programs now for pediatricians who want to be clinical pharmacologists. That’s a big difference. They may or may not elect to train in an adult-focused program, but there is at least the option to train in a pediatric program now if they wish to. I think that’s a big, big difference.

In terms of mentoring, as you mentioned, I retired from full-time work, and then a couple years later was invited back as a research mentor. I did that for the next, what, 6 or 8 years. I have to say, that was one of the most fun and enjoyable things I’ve ever done because I was able to focus on that and not have a lot of administrative things demanding my time or clinical things demanding my time. To interact with bright, young, highly capable people, who were frequently working in areas where I had no special expertise, but where I could brainstorm with them, learn from them, provide them with insights into research approaches, research techniques, and engage in sort of a Socratic interaction with them was really extremely fun, really enjoyable. I think one of the things that helped me a lot was the experience I had with my mentors years ago. We all make that change during our career. If you’re in a teaching environment and academics, you should pay it forward from where you benefitted, and then try to contribute to the next generation. That’s so essential to the development of the next generation. But I have to tell you, one of the most enjoyable things I’ve ever done was coming back and working with people on their individual research projects. Just a couple weeks ago, I got an email from one of the young faculty now at Children’s Mercy, sending me a copy of one of his abstracts that has been accepted to a meeting and that I helped develop the protocol for. He carried it forward to successful work and is presenting it around the country now. Those are the kind of things that really are fulfilling, to see that take place.

[break in audio]

DR. NEVILLE: Ralph, I would like to pick back up and circle back to talk a little bit about your tenure as chair of the Committee on Drugs for the American Academy of Pediatrics. By the way, I think it’s interesting, historically, that your mentorship has helped lead me to have the honor of chairing the committee, so thank you for that. You shared some stories with me that I think are historically very interesting, and I wondered if you could talk about those.

DR. KAUFFMAN: Okay. In various roles, I spent probably 17, 18 years interacting with the committee, either as a member or a consultant or a
liaison from the section, and then the last 4 years I was the committee chair in the early 1990s. When I became chair, I thought the most important thing the committee should do going forward was to advocate for the passage of legislation that would assure that children were included in studies of new drugs. I’ve talked about that at length.

In addition to the usual commentaries and work the committee does, the other thing that was a significant historical event, I think, was the role of the Academy, the Committee on Drugs, and the Committee on Infectious Diseases during the Reye syndrome epidemic, and the controversy around aspirin’s relationship to the risk of Reye syndrome. Reye syndrome occurred in epidemic proportions from about the mid-1980s into the 1990s and caused a number of deaths and also permanent injury to young children.

Early in that epidemic, a paper from a young public health service officer named Karen [M.] Starko appeared in Pediatrics, describing a small case-control study that suggested that aspirin, and possibly other medications, might be contributing to the risk of Reye syndrome. This raised an enormous amount of interest and controversy and led to a series of larger case-control studies over the succeeding years to try to sort this out. The overriding question for the practicing pediatrician, and policy-wise for the Academy, was whether to recommend to physicians and parents that aspirin not be given to children with febrile illness. Of course, there were alternatives. Acetaminophen was available at that time. I don’t think ibuprofen was yet available at that time for young children. But this connection with Reye syndrome and aspirin was highly controversial because the dominant antipyretic used at that time was aspirin, children’s aspirin. It was highly promoted by the pharmaceutical companies who made and marketed aspirin, and highly promoted for this use. It was a direct threat to their marketplace. This resulted in 4 additional case-control studies over the ensuing years, 2 of them in Ohio and 2 in Michigan. All of those studies continued to show a statistical association between aspirin use during a febrile illness and a risk of Reye syndrome.

The Academy was struggling to decide what their policy should be. The Red Book committee [Committee on Infectious Diseases] and the Committee on Drugs, early on in this controversy, took a position that the Academy should encourage physicians and parents not to use aspirin. This was fought very aggressively by the aspirin industry in a way that reminded me of the tobacco industry fighting the issue around tobacco and lung cancer. I think there have never been epidemiologic studies gone through with a microscope to the extent that these case-control studies were over an approximately 5-year period. Everything possible was done by the aspirin industry and their
supporters to try to discredit those studies. They recruited a number of very credible academic pediatricians to help argue their case, as well. Then on the other side there were many credible pediatricians who felt that aspirin should not be used in children and that the Academy should come out with that position. The Academy was in a difficult place because they didn’t want to make a recommendation that would be detrimental to children in terms of depriving them of an effective antipyretic. At the same time, they didn’t want to be caught in a position of supporting use of a drug that might ultimately be proven to be detrimental. So, it was a very difficult position. The decision sort of rested on which direction we should err. The 2 committees came out with strong draft position statements against aspirin use for children with febrile illness. The Academy leadership was reluctant initially to approve these for publication. In fact, one publication of AAP News was withdrawn under threat of lawsuit by the industry the day before it was to be distributed because it contained a position statement to the effect that aspirin was not recommended for children with febrile illness.

Subsequently, an additional large case-control study was completed that was actually funded by the aspirin industry. It showed the strongest correlation between aspirin and Reye syndrome of any of the studies that had been done to that point. That pretty much put the issue at rest. To the Academy’s credit, the Academy eventually approved publication of the Red Book committee and the Committee on Drugs joint statement. Aspirin use for children’s febrile illness then plummeted, and the labeling was changed. A warning statement was added to all aspirin products to not use them in adolescents and children with febrile illness. The story ended there. This was a major debate over a period of years with multiple hearings, multiple scientific meetings, a great deal of argument at national meetings and in the literature, and was a time of great drama and extremely difficult decision making by the Academy leadership.

DR. NEVILLE: Ralph, when we talked about this in the past, you told me a story of having to get on a plane very suddenly because of, I think, lawyers from the aspirin industry showing up at the Academy headquarters.

DR. KAUFFMAN: I mentioned that the Academy was undergoing their decision making under threat of liability lawsuits from the aspirin industry. While I was on the Committee on Drugs, one morning I was sitting at my desk getting ready for the day’s activities and I received this call from Jean [D.] Lockhart, who was then the staff person for the Committee on Drugs. This was in the middle of the ongoing controversy about Reye syndrome and aspirin that the Academy was embroiled in. Jean Lockhart said, “Ralph, can you get on a plane and come to Chicago this morning? There are 5 lawyers
here who are meeting with the Academy president and several Academy administrators, and we need somebody here who can provide us some scientific medical background on this and try to help them through this.” I didn’t know what I was in for, but I dropped everything and hopped a plane. I was working in Detroit at the time, so it was only a 55-minute flight. I flew down to Evanston [Illinois] and went to the Academy offices. It turned out that I really wasn’t needed. The meeting took place that morning. They preferred I not be involved in the meeting, and so I waited around the Academy for most of the day. Once the meeting adjourned, I flew back home, but I never participated in that meeting. I was told unofficially that the threat of litigation was clearly expressed at that meeting and created a very difficult decision-making environment for the Academy at that point in time.

DR. NEVILLE: That was something you anticipated when you joined the Committee on Drugs? [Laughs]

DR. KAUFFMAN: Not at all.

DR. NEVILLE: You have done many, many, many things, and we’ve been trying to sort of distill what has been memorable for you and some of the more salient activities. We’ve talked a lot about the discipline of clinical pharmacology, and you had quite a bit of service on the American Board[Inc.] of Clinical Pharmacology. I would like it if you could comment on that and maybe the evolution of that and what that has been like for you.

DR. KAUFFMAN: I’m not very familiar with the early history of the Board, and there is a history there to know. I served on the Board, I think, for approximately 6 years, and was chair of the Board the last several years. I enjoyed that activity. This is the examination board for clinical pharmacology for candidates who finish fellowships. One of the enjoyable things, and very challenging things, was preparing the exam each year. I obviously was only one of several people who, each year, submitted questions for this. One of the things I learned through this experience was that it’s much harder to write good questions than it is to answer good questions.

DR. NEVILLE: That’s true.

DR. KAUFFMAN: One of the things that we went through during my tenure on the committee was attempting to get the Board approved by the American Board of Medical Specialties. The Board had always been an independent board and had not been a member of the American Board of Medical Specialties, and we felt that it had matured to the point, at that time, that we should be able to do that. So, we spent several years planning and
preparing an application to the American Board of Medical Specialties for inclusion there. We suggested that it be a sub-board of pediatrics and internal medicine and psychiatry and obstetrics/gynecology, similar to what the toxicology sub-board is. We went through the entire preparation review process, which is an enormous amount of work. Of course, there were several other people on the Board who led the charge on this. One was Darrell [R.] Abernethy at Maryland. We submitted the application, and it underwent review.

It was ultimately denied, and the reason for denial was that the discipline of clinical pharmacology did not deliver a unique clinical service that required unique expertise that would qualify it as a sub-board of a general medical specialty. We disagreed with that, but at that point, we dropped the application attempt. To my knowledge, the Board has not pursued it subsequently. I think this is a part of the perception that clinical pharmacology as a discipline is neither disease- or organ-oriented, and so it was hard for the American Board of Medical Specialties reviewers to see it as something that would deliver a unique clinical service to patients. We both know that that's true, that there are clinical pharmacologists every day who deliver unique clinical services. But it doesn’t fit into the paradigm that currently is a part of the qualifications for American Board, so it still exists as an independent board.

DR. NEVILLE: Ralph, I’m going to push a little bit and ask you, that was around the year 2000, I think.

DR. KAUFFMAN: It was a little later than that because it was close to the time that I retired. So, it was probably in the first half of the 2000s. I don’t remember exactly.

DR. NEVILLE: Maybe 10 years ago. I can check and look back.

With the evolving super-subspecialization of medicine and the evolution of the discipline, is it ever worth trying to apply again? What are your thoughts? I think we’ve talked a lot about clinical pharmacology as the “orphan discipline” because of the very reasons you just said. We’ve also talked about how perhaps the best model for training is a physician trained in a specialty, and then doing a combined fellowship, which, to me, would maybe lend itself to this being a sub[specialty]. With how medicine is changing, what are your thoughts on the Board perhaps pursuing that again, because you were there when it was denied.

DR. KAUFFMAN: Right. I think there’s an answer to that at several levels. One level is that I think it would be appropriate to make it a subspecialty
under the American Board of Medical Specialties. One advantage of that is that it would provide an increased incentive and reward for people to go through that extra training. I think there would be a clear advantage to it. It would also promote the discipline on the clinical level. It’s frequently perceived as a uniquely or exclusively research discipline, but it really doesn’t need to be. So, I think there would be a big advantage in doing it.

I think the other level is the practical level. I don’t know at this point in time if the perception of the discipline has advanced to the point where the people who review applications would accept it as a valid discipline for board certification. I think that would have to be negotiated. I don’t think an application should be submitted again until there are preliminary negotiations with the American Board to assure that the review would likely lead to approval, because it’s too much work to do it. I honestly don’t know whether there would be support for that at this point in time or not. I think it would be a good idea, but I just don’t know if it’s realistically possible at this point.

DR. NEVILLE: It’s a shame because it is such an integral discipline.

DR. KAUFFMAN: Yes, it can be. It’s sort of like genetics. It’s such a prominent part of medical practice. And the pharmacotherapy of patients is becoming increasingly complex as the training in medical school and residency is decreasing in this area. Physicians are continuing to be trained, both at the medical school and the graduate level, with inadequate training about the proper use of medications, the nuances that really help you out in the complicated situations, the understanding of drug interactions, and the pharmacogenetics of drug therapy. All these things that are so important now are not being adequately taught in medical school and primary residencies. As pharmacotherapy is becoming so much more complex and targeted and personalized, we’re not preparing the future generation of practitioners to use that information, so I think this is a discipline that desperately needs to be included in postgraduate education. There needs to be a cadre of subspecialists that can do that teaching and continue to do that research, and they need to be rewarded with professional recognition for their level of expertise.

DR. NEVILLE: I couldn’t agree more.

Ralph, you’ve done so much over your career and you’ve contributed so much. I don’t think you even realize the gravity of what you’ve contributed. For example, we haven’t even touched on the editorial boards you’ve sat on, and to me, having the honor of doing that myself, that’s an incredible contribution to the field. For
example, you were on the editorial board of the *Journal of Pediatrics*. I’d like to hear just a little bit about your favorite parts, or least favorite parts of that, and how you think the literature has advanced for children. Knowing you as a person, I’m guessing it was very enjoyable to you to serve on those boards because it’s acquisition of knowledge, but I don’t want to put words in your mouth. I want the readers of this to understand the scope of what you’ve done and how that was for you.

**DR. KAUFFMAN:** I think the answer, in terms of enjoyment, is yes and no. As you know, there is the enjoyment of seeing a lot of new information before it is available to the general population, so that’s a real learning experience. Then there’s the disappointment and chagrin of seeing papers that should never see the light of day and trying to figure out how to critique them in a way that isn’t going to be destructive and, hopefully, at least in most cases, help someone construct the paper into a publishable manuscript. I think one of the really important roles or responsibilities of a reviewer is to do a critique that, even if you don’t think the paper is publishable at this point or in this form, can tell the authors how to revise the paper so that it is publishable and will contribute to good medical literature.

I think the other frustration in being a reviewer—and I’m sure you’ve experienced this, too—is knowing that, in a journal like *Pediatrics*, only 10% to 15% of manuscripts are ever going to be accepted for publication. You may see something you think really ought to be out there, but you’re not sure the editor’s going to accept it, even if you give it a positive review and support it. There’s the frustration sometimes of seeing a paper that you think really ought to go in, but doesn’t, at least not in that journal. It may get published eventually someplace else.

Another thing that I think is extremely helpful, and I would encourage people to do this, particularly people who are full-time academic medicine, is that every time they get a chance, be a reviewer for manuscripts. It also teaches by experience about writing and writing style and what is a good paper and what is a bad paper. One of my mentors, whom I never worked directly with, but I learned to know him and attended several of his writing conferences, was Joe [Joseph Morris] Garfunkel who was editor for many years. He would give 2- to 3-day writing seminars around the country that were very informative. He also gave me from time to time when I was a reviewer, feedback from the editor’s point of view, which was instructive. Writing, for me, was never easy. Maybe that’s the way it’s supposed to be.

**DR. NEVILLE:** Can you comment on that? Because I think there’s a perception that you just bang out a paper, and that in some ways, research is easier
in that way than clinical medicine. I was an English major, but I struggle with scientific writing, and I think a lot of our junior and mid faculty do. They see prolific authors like you and think, well, maybe it came easy to him, and it’s just not to me. From what we’ve talked about, you’ve had some amazing mentors, but can you talk about your struggles with that?

DR. KAUFFMAN: Writing has always been work for me. I enjoy it when I get into it. Especially if you have good data, writing a paper is really fun. I’ve always viewed writing a scientific paper sort of like doing a sculpture. The rough draft is the chiseling out the general form of the sculpture, then you organize it a little better and refine it a little better, and eventually you get to the point where you’re trying to decide exactly how you want to say this particular sentence. Sometimes I sit for a long, long time deciding how to say something and nuance it so that it will make the impression that I want. I think one of the mistakes young writers make is that they don’t pay enough attention to organization of thoughts. You need to lead your reader’s mind through your ideas and what you’re trying to tell them, and that takes intense attention to organization. There can be a dozen ways to say something or to fashion a paragraph, and you need to work and work to say it as concisely, but as precisely, as you possibly can. People fall down in that area, too.

DR. NEVILLE: Back to what we’ve talked about previously, we’re spoiled now because it’s all word processing, right?

DR. KAUFFMAN: But it’s so nice.

DR. NEVILLE: Early in your days, you had to retype, didn’t you? [Laughs] Amazing you still continued to work on it.

DR. KAUFFMAN: We used lots of [Bic] Wite-Out. [laughter]

DR. NEVILLE: We’ve talked a lot about your experiences with the FDA and your work with the FDA, but I would be interested in your perspective of how the FDA has evolved because I think it’s of historic importance. We were talking about the laws in 1962 versus now. There’s no sunset. BPCA and PREA are clear. There is the [U.S. Food and Drug Administration] Office of Pediatric Therapeutics. So, I think the agency has really grown prolifically and come a long way. You were there for that, so I would be interested in your perspective.

DR. KAUFFMAN: Well, I was there for the very early aspect of it.

DR. NEVILLE: Yes, but I mean you’ve been a part of the field in clin pharm.
DR. KAUFFMAN: I’ve sat on the other side, as an investigator. I’ve interacted with the FDA and watched it. And you’re right, the FDA is, in terms of advocating for and reviewing and dealing with pediatric new drugs and studies and pediatric indications and safety, an entirely different agency from what it was 30 years ago in terms of level of expertise in pediatric matters, organizational structure, infrastructure to deal with pediatric issues, and attitude about pediatric issues. There was an era for a long time at the FDA where pediatrics really wasn’t a priority, and you couldn’t get their attention about pediatric method. That’s changed totally with the legislation over a 10- to 15-year period, the reorganization at the agency to respond to pediatric pharmacology and to the new legislation, and the kind of people who have contributed leadership in the pediatric aspects. All of those things have completely changed the environment at the FDA for reviewing and handling pediatric aspects of new drug applications coming through, and supplements, and so forth—pediatric issues in general. You can go to the FDA website and look at this and see the data about what has happened in the last 15 years that has changed the whole environment for pediatric pharmacology research and the approval of and labeling for drugs for kids. That has to have impacted pediatric practice.

In some ways, the agenda at the FDA hasn’t changed since I was there in 1966 to 1968. They are always being criticized and they’re always underfunded for what their mandates are. That agenda has never changed. They’re almost always short-staffed for parts of their agenda and their mandates. There’s always a political constituency that says they’re not approving drugs fast enough, and a political constituency that says they’re approving unsafe drugs because they’re doing it too fast. They deal with that politics, and they were dealing with it when I was there. That politics has never changed and probably never will. They walk that tight rope and deal with all those issues. But in terms of pediatric issues, they have made enormous strides. It’s a whole different environment there from what it was 30 years ago.

DR. NEVILLE: Again, I’m sensing a recurrent theme. One, that people like me and younger take for granted, right? For example, if I’m bringing a drug forward, I know there’s a pediatrician at the FDA. I think historically it’s important to realize that that has not always been the case, and in fact, it’s not that long ago that it wasn’t the case.

DR. KAUFFMAN: And there’s a pediatric committee there that’s overseeing the whole thing and can help you resolve it. It used to be that, without the pediatric committee and some of the other structure that now exists at the FDA, the individual review groups were pretty autonomous in terms of their
decision-making at the level of reviewing, and there was no pediatric advocacy at all in most of those individual review sections. Both having more pediatric expertise in most of the review sections, as well as the committee level, has changed the process enormously. And I should say, pediatric advisory groups [Office of Pediatric Therapeutics Pediatric Advisory Committee], too, made a big impact.

DR. NEVILLE: Right, so actually I wanted to touch on that, because you’ve been a part of the Pediatric Advisory Committee.

DR. KAUFFMAN: Some, in the past.

DR. NEVILLE: In the past.

DR. KAUFFMAN: Not currently.

DR. NEVILLE: Do you think there’s been a similar evolution of expertise on the industry side? We’ve talked a little bit about the PPRU doing industry studies. Was there a consequence of that, of pharma [the pharmaceutical industry] gaining expertise? Compared to when you started out, and then more recently, how do you think industry has evolved?

DR. KAUFFMAN: With the change in the laws, that encouraged pediatric studies and rewarded the pharmaceutical industry. Yes, at least a number of the larger pharmaceutical companies responded to this and developed increased pediatric expertise, as well as, in some cases, unique pediatric programs within their companies. Others did not so much. Others tried to look like they were doing that, but really didn’t. So, it’s been a mixed bag. Some of the larger companies have really taken major steps to not only build pediatric expertise in-house, but pull in more pediatric expertise in their protocol development, their advisory groups, and so forth. That has changed significantly, but not consistently across the board. But it’s happened enough that it’s made a big difference in both the number of studies, as well as the quality of studies. Early in this process, the quality of studies, as you know, coming out of industry and the protocols were pretty dismal. They were ramping up the same way as everyone else. So now the quality of studies coming out, by and large, are much better in terms of pediatric aspects of the studies and paying attention to pediatric issues and age group-defined issues from what they were initially. There are, as you know, some laughable examples that I won’t go into.

DR. NEVILLE: [Laughs] Cut and paste, and doing pregnancy testing on a 9-month-old. I think we’ve shared some of those foibles.
DR. KAUFFMAN: I think it still occurs occasionally, but it’s much, much less common than it used to be. The protocol quality, I think, is considerably better.

DR. NEVILLE: One question I have for you is sort of two-fold. Where do you see pediatrics going in the up-and-coming years, whether it’s 10, 20, 50 years? And where do you see pediatric clinical pharmacology going? Where would you see their interaction? We talked a little bit just now about the boards. Where do you see pediatrics going? Where do you see peds clin pharm going, and do you see them integrating, or what do you think the relationship will be?

DR. KAUFFMAN: I think incorporating clinical pharmacology into pediatric training is still going to be a constant struggle in most places. I think there will, probably for the foreseeable future, be a relatively small group of medical schools or centers that provide this service, but I think it’s going to be greater than in the past.

I think another thing that’s going to happen is that, as people are trained—like you have been at Kansas City, and a few other centers training people who have clinical specialties combined with clinical pharmacology formal training—over time we’re going to see more of an integration of the knowledge base and tools of clinical pharmacology into different clinical subspecialty areas. That will indirectly impact resident and fellow teaching by those individuals who have that integration. But I don’t see it being a dominant influence in the foreseeable future. I don’t say that negatively. I just think that’s a reality.

In terms of pediatrics in general, what I see happening is so much over the last decade particularly, a significant shift from the biology of pediatrics to the sociology and behavior of pediatrics, particularly the sociology of pediatrics, particularly in general pediatrics. The training, and if you look at the articles in Pediatrics, in Journal of Pediatrics today, they’re dominated by sociology and behavioral issues, as opposed to the biology of disease and so forth, and also a lot of policy debates. [The] New England Journal [of Medicine] is that way, too. Medicine has become very politically and sociologically oriented, which has diluted to some degree the biology of the medicine. That may be necessary. I’m not arguing good or bad. I’m just saying I’ve observed that as a trend over time, and that affects pediatric training.

The other thing that’s happened, not only in pediatrics, but across medicine in terms of resident training, is a gradual shifting to a shift-work model as
opposed to the physician who is the person’s physician, and I think that’s detrimental to the practice of medicine. I know that the pediatric board is now re-reviewing training scheduling and issues and rethinking what has happened over the last decade. But I think that if physicians all move to shift-based work, it’s going to significantly influence the doctor-patient relationship and the culturalization of the relationship and influence the continuity of care. I don’t know where the balance is, but I think that right now the pendulum has swung to one extreme. We need to center it again.

DR. NEVILLE: As a follow-up, I was going to ask you, how you think that impacts clinical research? Because we talked about the fact that we’re in the era of “omics”, right? Genomics. We’ve made huge strides in sequencing the genome, and now we know about metabolomics and proteomics. Developmentally, there has to be changes in that. But if we’ve shifted because of other forces, how do you think what we’ve been talking about affects our pursuit of knowledge in those arenas, or even clinical and translational research within the discipline, or pediatrics?

DR. KAUFFMAN: I think on the positive side, those advances, both in tools, as well as knowledge, have and will continue to have, a profound impact on pediatric knowledge, but it takes a generation or 2 for that knowledge to seep into everyday clinical practice. There has to be a concerted effort on the part of medical educators to understand what needs to be included in the medical curriculum across the spectrum of medical education from undergraduate to graduate, to set priorities, and to be sure that people who are being trained are being exposed at least to the level they need to incorporate this new knowledge and tools into their practice, because the omics revolution is changing medicine across the board. Unless we incorporate that from medical school on forward, we’re going to be training people who aren’t going to be able to cope. Of course, medicine should also train us to continue to learn, because as is true with your generation, most of what I learned in medical school was obsolete long before I finished my career. We have to continue to learn every day by our interaction with people who know more than we do and by literature and all sources of new information coming to us. We have wonderful tools now for continuing education, which makes it more efficient in many ways, but it’s easy to be overwhelmed, also.

DR. NEVILLE: Yes, the societal shifts. You and I talked about this. There are always more and more demands on your time.

DR. KAUFFMAN: Another thing you’re well aware of that has come in is the regulatory changes that have imposed themselves on medicine and require a great deal of physicians’ time. Also, tools that are supposed to save
time, like the electronic medical record, which some people complain actually
takes more time right now in the generational transition to that. There’s a
generation of medical trainees coming through now who will never
experience anything other than that, so to them it’s going to be second
nature. They wouldn’t know what to do with a paper record. But for the
generations that are transitioning, it slows everyone down a little bit.

DR. NEVILLE: My bias, having been in the middle, is that you worry
because of the shifts. Like you said, with all the regulation, it becomes more for
billing than for the patient. There’s a concern.

DR. KAUFFMAN: I had to laugh. A few years ago, I was sitting in a meeting
where they were talking about some novel changes to the residency training
program and making rounds. When I was a resident, we made rounds with a
chart rack. We had a rack on wheels with all the charts hanging on it. We
went bedside to bedside, pulled the chart out, looked at it, talked about the
patient, wrote the orders, and put the chart back on the rack. The
revolutionary thing that was going to be tried was that they were going to
provide everyone an iPad. You would carry your iPad with you on rounds,
actually look at the patient’s chart on rounds, and put your orders in on the
iPad while you were on rounds. And it was revolutionary. [Laughter] I
thought, 30 years ago we did this, only we did it on paper and not an iPad,
but it’s the same thing.

DR. NEVILLE: Yes, it is.

We talked a little bit about how the center grant and NIH funding was
instrumental in your start, in getting some momentum going. With funding rates
around less than 10% and all we’ve talked about, one of my questions to you is,
do you think physicians entering into pediatrics, pediatrics clin pharm, both, can
have as worthwhile a career as you have had? We’ve talked a lot about how things
are different, but what would you say to that?

DR. KAUFFMAN: I think they can have as worthwhile a career, certainly. It
depends on their interest and their effort. It’s not going to be as easy to get
federal funding as I had. That was a time when it was sort of a heyday of
federal funding at the NIH. As I recall, the funding levels were in the range of
25% to 35%. You could submit a grant and have a pretty good chance of
getting funded. I was exceptionally fortunate to be able to do that right out of
fellowship. It was a combination of the funding patterns at the NIH at the
time and being in an institution where they had a center where I could
piggyback on a center grant. I wouldn’t have been able to do it with an R01
[NIH Research Project Grant (R01)] at the time the same way.

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I think funding will continue for the foreseeable future to be very challenging, very difficult. I think people are going to have to look for funding from other than NIH sources. I think mentorship becomes inordinately important this way—for a young faculty person to piggyback on an established lab and be mentored into the funding mechanisms that exist early in his or her career. You can’t compete there unless you have people who are going to lead you down the path and help you do it. I think that is so critical. So, I think there are going to be continuing challenges. It’s not going to be nearly as easy to get the funding as it was when I started out, but I think they can have very fulfilling careers. The danger is that they’re going to get discouraged and give up on the research aspect of their career because clinical work is so immediately rewarding, but with research, you have to deal with delayed rewards. It’s just the nature of the business. If you’re constantly being discouraged by the inability to get funding, regulatory constraints, and institutional constraints, it’s so much easier to just migrate into clinical work and get your rewards there. So, I think the big danger is losing people from a clinical research career because they are frustrated by that aspect, as well as others. Mentoring and bringing people along with you becomes so critical.

DR. NEVILLE: I think at least my generation is feeling the pressure of almost “buying your time.” Not only is it the gratification of having the direct patient care, but with RVUs [relative value units], the pressure to produce on the clinical side, as well. I would like to hear your comment. We’ve talked about the pressure of the balance, but did you feel that same pressure?

DR. KAUFFMAN: By that time, I was doing very little clinical work anymore. I really never had to deal directly with RVUs and everything that people are dealing with today, thank goodness. But I can understand that that is a tremendous pressure. So, I didn’t experience that. It wasn’t part of my difficulty in selecting. I think the pressure to produce on the clinical side creates an enormous responsibility on the part of training institutions and academic institutions to find a way to pick a subgroup of individuals, and then find a way to provide them shelter from that. Otherwise, they’re not going to be able to be successful in an academic research career. Now, I don’t know exactly how institutions are going to do that, because every institution is different and has its own fiscal challenges, but they need to do several things. One is that the institution has to have mentors who can, as I said, bring people along and help them. The institutions that are competitive get the funding. Institutions need to keep researchers from getting discouraged and give them the support they need to get established in their career so they don’t give up. Secondly, institutions need to find ways to shelter researchers,
at least for part of their time, and not threaten them for doing this. They need to be rewarded for doing that. That’s a challenge for the institutional leadership, too. I wouldn’t want to be a dean today anywhere.

DR. NEVILLE: Or a CEO. [Laughs]

DR. KAUFFMAN: Yes.

DR. NEVILLE: Ralph, as you look back over your career, were there any periods in time that now you say were particularly difficult or challenging? And if so, or not, why?

DR. KAUFFMAN: Yes, there were periods of time where, on a day-to-day basis, I was very discouraged. When you go for several weeks and can’t get your assay to work and you don’t know what to do to fix it, and it’s jeopardizing your whole project, those are very discouraging times. Everyone in laboratory work goes through those periods. You have to just find help where there’s help and move forward. There were times where I was very disconcerted about the administrative aspects of the institution I was in. I didn’t agree with things sometimes, but I had to decide how to constructively deal with those. You learn from those experiences. You have to pick and choose what’s right for you to stay engaged in. It’s different for everyone. I can’t tell any specific individual, from my experience, “You should not do this” or “You should do this” in a given situation. But you need to be aware that there will be times, rough patches, where you feel angry and frustrated and like you’re at a dead end because of institutional conflicts and impediments. Hopefully, most of the time, you can deal constructively with those in one way or another.

Looking back, I don’t have any major regrets. I feel like I had a very fulfilling, rewarding career with a lot of variety in it. I think I could have been equally happy doing nothing but clinical practice. If I had any regret, it would be that I’d like to do it all over again and just do clinical practice. But I didn’t do that, and I can’t do it over again, so I don’t have regrets.

DR. NEVILLE: If you look back, what was your single greatest challenge? You and I have talked a lot about the struggle, because, like you, I love the clinical. It’s challenging to decide to leave that. What would you say your single greatest challenge was over your career, if you had to pick one thing? And then we’re going to talk about accomplishments.

DR. KAUFFMAN: I think probably the most challenging thing was trying not to get sidetracked or use up too much of my time in administrative
responsibilities. Everyone struggles with that. I wasn’t unique at all. I constantly struggled with that to try to make sure—and I didn’t always make sure—but to try to not get so consumed in time-consuming administrative stuff and nonproductive activity that I would lose focus or not really be doing what was important. Sometimes, on a day-to-day basis, it’s hard to keep your long-term focus. If there’s a particularly rough patch or confusing patch of life, it’s hard to keep your long-term focus.

I would encourage people to try and step back. If they’re particularly frustrated or having a difficult time, step back and think about what their long-term focus is, and then try to create a personal trajectory that will help them follow that. The other thing I would say, based on my own experience, is to be ready for surprises and for making decisions on whether or not you’re going to take advantage of the surprises and opportunities that come along. They will come along from time to time, things that you didn’t plan for.

DR. NEVILLE: That was going to be my next question for you. How much do you think you picked, and how much do you think picked you?

DR. KAUFFMAN: Well, it was a combination. It wasn’t either-or. In terms of moving from the University of Kansas to Wayne State in 1979, I think I was ready for a move if there was an opportunity because I had recognized my limitations there. That was an example of an imbalance with administrative responsibility. Very early in my career, I suddenly found myself as a vice chairman of a pediatrics department and I recognized it was too early—I shouldn’t be doing that. There was not an easy way to get out of that without doing something radically different. I was ready at the time, and then the opportunity came along. So, that was an opportune thing for me and for the other institution.

Prior to that, the selection to go to the FDA was a total out-of-the-blue thing that was never even remotely on my radar screen. I wasn’t even aware of such a possibility. If that hadn’t come up, I would have had a totally different career trajectory, and my life would have been very different. Not worse, probably, but different. So, I’m thankful that happened, although at the time I thought it was a major interruption in my career and life.

The opportunity to go back to Kansas City again was something I hadn’t anticipated at all and wasn’t looking for. It was a very difficult decision to make because it was going from a situation of relative comfort and security to something that wasn’t secure at all in terms of how it was all going to turn out eventually. Fortunately, it turned out very well, thanks to the institution,
to the good people who joined me in going there, and all of the other people who supported the effort. But at the time, I had no assurance that it was going to pan out.

DR. NEVILLE: So, there was risk?

DR. KAUFFMAN: Yes, there was a fair amount of risk.

DR. NEVILLE: I think we often don’t talk about the fact that in your career there are risks.

DR. KAUFFMAN: There are risky times, and you have to balance. Physicians are generally trained to deal with risk-benefit, but we don’t always apply it to our personal lives very well.

DR. NEVILLE: That’s true. Another thing we don’t often talk about in research is the “intentional no.” We were just talking about developing your own trajectory. Do you recall intentionally learning how to say no because particular projects or opportunities were a distraction from what you wanted to do, or did it just sort of fall into place?

DR. KAUFFMAN: Oh, no, it rarely just fell into place smoothly. People are always making choices, and it’s important for people to do this. I’ve told people this before. You need to decide, at whatever point you are in your career, what’s important for your career development and you, and then for the people around you secondarily, and thirdly, for your institution. You need to think through the pros and cons, the benefits and risks, and the downsides of any major decision. I think saying no has got to be always an integral part of your process. I’m sure there were times I’ve said that I didn’t want to do this, but there were times I didn’t have that option, too. One that comes to mind, that stands out, is when I was at Children’s Hospital Michigan. That institution houses the regional poison control center for eastern Michigan. The poison center was part of my clinical pharmacology division. The director of the poison center was a wonderful person named Reggie [Regine] Aronow. If you look at poison center literature prior to 1985, you’ll see a lot of stuff with Reggie’s name on it. She was an amazing person. She had been head of that poison center for decades. I was on vacation down in Arizona one summer and I got this phone call. “Dr. Aronow has turned in her resignation.” I had no warning, nothing. I hadn’t really paid close attention to the poison center because it was under good management. I couldn’t say no, because it was a part of my operation. Until I could recruit a new director, I had to step in and be the interim in addition to everything else and I didn’t want to do that. I had to train technicians. I had to get technicians
ready for their exam. I had to submit the renewal stuff for the poison center certification right away by the end of that summer. There were just oodles of stuff to do that I had no interest at all in doing and no time to do, but I had to do it. That’s an example. There are times when you can’t say no because it’s too important to do it. But there are times when it’s appropriate to say no, also. That’s a long answer to your simple question.

DR. NEVILLE: No, because I don’t think it’s simple. I’ve learned the hard way that where you say no is just as important as where you say yes.

DR. KAUFFMAN: You’re correct, yes, it is.

DR. NEVILLE: We’ve talked about how you could have been, potentially, equally happy as a clinician and you have no regrets. Is there anything you would have done differently in looking back?

DR. KAUFFMAN: The one thing I would have done differently, and it really wasn’t obvious at the time, is that I would have done a subspecialty fellowship in addition to my clinical pharmacology. At the time, it wasn’t an issue for me, but subsequently in my career, it would have been an advantage, but it was too late by that time to go back and do a subspecialty fellowship. I would encourage all medical people, physicians who are going to do clinical pharmacology, to do a combined fellowship, because having a clinical subspecialty along with your clinical pharmacology expertise is really very, very advantageous and makes you extremely marketable.

DR. NEVILLE: Interesting. Is there any one in particular that you think you would have done?

DR. KAUFFMAN: I probably would have done either neonatology or GI [gastroenterology], probably.

DR. NEVILLE: Interesting.

DR. KAUFFMAN: I did some of that kind of practice without formal training for short times early in my career because there wasn’t anyone else there to do it and I enjoyed it. I would have been much better off had I had a clinical fellowship along with my clinical pharmacology.

DR. NEVILLE: We’ve talked about how much you’ve done in a myriad of things. For you, in looking back over your career, if you had to pick one thing, what do you think your single greatest accomplishment has been? And it doesn’t have to be a project. It could be having your children. I just am interested to
know.

DR. KAUFFMAN: Well, the kids are a whole different dimension.

DR. NEVILLE: Of course.

DR. KAUFFMAN: They’re the most important thing I’ve ever done. The career and whatever I’ve done professionally pales to having kids, and now grandkids. It’s really the greatest thing that happened.

But aside from that, I don’t know. I guess there are 2 things looking back that give me a great deal of satisfaction. One is being a part of getting the legislation passed for assuring that kids would be incorporated, included, in new drug development. The other thing was seeing the development over 15, 20 years of the clinical pharmacology unit at Children’s Mercy hospital. That has been a source of great satisfaction to watch that take place and see how successful it is.

DR. NEVILLE: I have 2 final questions. One is, if you had one piece of advice to give trainees or young pediatricians based on your experience, what would that be?

DR. KAUFFMAN: It would be very general. I guess it would be, try to know and understand yourself as well as you can. Get your education and select training places where there are good mentors for the areas of interest for you. Mentors are critical. And then pick the area of work that’s your passion. It’s too much work to do medicine for a career without enjoying it, so pick what’s your passion. Whether it’s clinical or teaching or research or whatever, or a mix of that, pick what’s your passion.

DR. NEVILLE: That’s fantastic. What’s next for you? We’ve talked a lot about your pursuit of music and me trying to suck you back into mentoring or helping with the FDA. What’s next for Ralph Kauffman?

DR. KAUFFMAN: Well, in about 30 minutes, I’m going to have lunch. [Laughter]

There comes a time when you have to gradually allow yourself to step away from medicine, as enticing as it is. I still work with the Rocky Mountain Poison [and Drug] Center, on a research project, but that takes only maybe 8 or 10 hours a month.

DR. NEVILLE: And you still mentor, sort of?
DR. KAUFFMAN: On a very limited basis. Having moved away from Kansas City, it’s very remote now.

My real passion now is my music. I play double bass with 2 string orchestra groups in Ann Arbor and enjoy that immensely. I plan to resume my music lessons later this fall and also sing with a group. I’ve made music my retirement vocation and get a great deal of enjoyment out of it. I spend more time with Schubert and Mozart and bluegrass than I do with medicine nowadays, and it’s great.

DR. NEVILLE: That’s wonderful.

Well, Ralph, it’s been an honor for me to be able to talk to you and to review the enormous contributions you’ve made to clinical pharmacology and me personally. On behalf of the Academy, thank you for spending this time with me, and thank you for all you’ve done. It’s been an honor.

DR. KAUFFMAN: Thank you, Kathleen. It’s an amazing honor to be selected to do one of these oral histories. I had no idea that this would be a possibility until I was contacted. And to have you do it was a special honor and a lot of fun doing it. I wish you and Greg [Kearns] the best in your new location and experience. I know you’ll have some wonderful years ahead. Keep in touch.

DR. NEVILLE: I will. Thank you.

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CURRICULUM VITAE

Ralph E. Kauffman, M.D.
Emeritus Professor of Pediatrics
University of Missouri-Kansas City
Retired June, 2006

ADDRESS
4080 Glacier Hills Dr
Kansas City, MO 64154

PERSONAL DATA

Date/Place of Birth: January 26, 1939
La Junta, Colorado

Marital Status: Married, Two Children
Wife, Laurel
Daughter, Janelle
Son, Craig

EDUCATION

1961 B.A., Bethel College, Newton, Kansas
1965 M.D., University of Kansas, Kansas City, Kansas

TRAINING

1966 Rotating Intern, Kansas City General Hospital, Kansas City, Missouri
1966-68 Surgeon, U.S. Public Health Service, Detailed to Food and Drug Administration, Bureau of Medicine, Arlington, Virginia
1968-70 Resident in Pediatrics, University of Kansas Medical Center, Kansas City, Kansas
1970-72 USPHS Post Doctoral Fellowship, Clinical Pharmacology/Toxicology, University of Kansas Medical Center, Kansas City, Kansas
FACULTY APPOINTMENTS

1970-72  Instructor in Pediatrics, University of Kansas, Kansas City, Kansas
1972-76  Assistant Professor, Pediatrics and Pharmacology, University of Kansas, Kansas City, Kansas
1972     Clinical Assistant Professor of Pediatrics, University of Missouri, Kansas City, Missouri
1976-79  Associate Professor, Pediatrics and Pharmacology, University of Kansas, Kansas City, Kansas
1976-79  Vice Chairman, Department of Pediatrics, University of Kansas, Kansas City, Kansas
1978-79  Director of Residency Training, University of Kansas, Kansas City, Kansas
1979-82  Associate Professor of Pediatrics and Associate in Pharmacology, Wayne State University School of Medicine, Detroit, Michigan
1982-95  Professor of Pediatrics and Pharmacology, Wayne State University School of Medicine, Detroit, Michigan
1995-2006 Marion Merrell Dow/Missouri Endowed Chair in Medical Research and Professor of Pediatrics and Pharmacology, Children’s Mercy Hospital and University of Missouri at Kansas City, Kansas City, Missouri
2.006-   Emeritus Professor of Pediatrics, University of Missouri at Kansas City, Kansas City, Missouri

HOSPITAL AND OTHER PROFESSIONAL APPOINTMENTS

1979-80  Associate Attending Physician, Children’s Hospital of Michigan, Detroit, Michigan
1980-95  Attending Physician, Children’s Hospital of Michigan, Detroit, Michigan
1982-95  Director, Division of Clinical, Pharmacology/Toxicology, Children’s Hospital of Michigan, Detroit, Michigan
1986-95  Director, Inpatient Pediatric Medicine, Children’s Hospital of Michigan, Detroit, Michigan
1986-88  Professional Director, Drug Assay/Toxicology Laboratory, Children’s Hospital of Michigan, Detroit, Michigan

1988-93  Vice Chairman for Clinical Affairs, Children’s Hospital of Michigan, Detroit, Michigan

1989-92  Medical Director, TDM/Toxicology Division, Damon Clinical Laboratories at the Detroit Medical Center, Detroit, Michigan

1993-95  Medical Director, TDM/Toxicology Division, DMC University Laboratories, Detroit, Michigan

1993-95  Vice Chairman of Pediatrics for Research, Children’s Hospital of Michigan, Detroit, Michigan

1995-2006 Chair, Dept of Medical Research, Children’s Mercy Hospital, Kansas City, Missouri

MAJOR PROFESSIONAL SOCIETIES

1971  Fellow, American Academy of Pediatrics
1972  American Association of Poison Control Centers
1972  American Medical Association
1972  Kansas Medical Society
1972  Wyandotte County Medical Society
1973  Kansas City Southwest Pediatric Society
1974  American Society for Clinical Pharmacology and Therapeutics
1977  American Society for Pharmacology and Experimental Therapeutics
1977  Society for Pediatric Research
1980  Michigan Chapter, American Academy of Pediatrics
1981  Midwest Society for Pediatric Research
1986  American Pediatric Society

LICENSURE AND BOARD CERTIFICATION

1965  Medical License, Missouri - Inactive
1966  Medical License, Kansas - Inactive
1967  Medical License, Maryland - Inactive
1979  Medical License, Michigan - Inactive
1971  American Board of Pediatrics
1994  American Board of Clinical Pharmacology

HONORS AND AWARDS
1974 Faculty Development Award in Clinical Pharmacology
Pharmaceutical Manufacturer’s Association Foundation

1981 Children’s Hospital of Michigan, Resident Education Award

1982 Pfizer Visiting Professor, Emory University

1983 Journal of Pediatrics Visiting Professor, University of Kansas

1984 Ittner Visiting Professor, University of Nebraska

1986 Visiting Professor, Department of Pediatrics, University of Texas Health Sciences Center, San Antonio, Texas

1987 Visiting Professor, Division of Neonatology, Baylor University, Houston, Texas

1990 Visiting Professor, St. Elizabeth Medical Center, Youngstown, Ohio

1993 Clinical Pharmacology Consulting Visit, The Children’s Mercy Hospital, Kansas City, Missouri

1993 Visiting Professor, University of Kansas, Kansas City, Kansas

1993 Visiting Professor, University of Minnesota, Minneapolis, Minnesota

1993 Visiting Professor, University of Illinois Medical School at Peoria, Peoria, Illinois

1994 Visiting Professor, Chinese Medical Association, Beijing, Shanghai and Guangzhou China

1995 Honor Citation Award, Pediatric Advisory Panel, U.S. Pharmacopeia

1995 Marion Merrell Dow/Missouri Endowed Chair in Medical Research, University of Missouri – Kansas City and Children’s Mercy Hospital

1999 William A. Evans Memorial Lecturer, Wayne State University, Children’s Hospital of Michigan

1999 Pfizer Visiting Professor, University of Utah

2001 Visiting Professor, UAMS-Arkansas Children’s Hospital, Little Rock, AR

2002 Visiting Professor, Department of Pediatrics, Baylor College of Medicine, Houston, TX
2004 Visiting lecturer, Guangzhou Children’s Hospital, Guangzhou, China, June, 2004.

SERVICE:

PATIENT CARE

1979-1995 Children’s Hospital of Michigan Ward Attending: 2-6 months per year
1979-1995 Children’s Hospital of Michigan In service consultation for Pharmacology/Toxicology
1995 - 2006 Children’s Mercy Hospital In service consultation for Clinical Pharmacology & Toxicology, 1 week/month

JOURNAL/EDITORIAL ACTIVITIES

Editorial Boards

1984-91 Journal of Pediatrics
1984-89 Pediatric Pulmonology
1993- Biology of the Neonates
1993-97 Drug Metabolism & Disposition
1999- Current Therapeutic Research
2000- Journal of Pediatric Pharmacology and Therapeutics

Regular Reviewer
American Journal of Diseases of Children
American Journal of Obstetrics & Gynecology
Developmental Pharmacology and Therapeutics
Journal of Pediatrics
Pediatrics
Clinical Pharmacology & Therapeutics
Pediatric Pulmonology
AMA Drug Evaluations
USP Drug Information for the Health Professional

Guest Editor
Pediatric Clinics of North America, 1981
Pediatric Annals, 1985

NATIONAL AND INTERNATIONAL BOARDS AND COMMITTEES

1975-93 Committee on Drugs, American Academy of Pediatrics
1989-93 Chairman, Committee on Drugs, American Academy of Pediatrics
1975- USP Advisory Panel on Pediatrics
1978 Ad Hoc Member, Pharmacology/Toxicology Study Section, NIGMS
1979-84 Executive Committee, Section on Clinical Pharmacology and Therapeutics, American Academy of Pediatrics
1980 Wayne State University School of Medicine, Representative to 1980 Quinquennial Meeting of U.S. Pharmacopeial Convention
1981-82 Member of Centers for Disease Control Reye Syndrome Working Group
1981-83 Chairman of Section Committee, Clinical Pharmacology and Therapeutics, American Academy of Pediatrics
1981 Site Visit Team, NIGMS, University of Minnesota, Minneapolis, Minnesota
1982 Special Study Section, Toxicology Section - NIH
1982 Site Visit Team and Special Review Committee, NIGMS, Cornell Medical Center, New York, New York
1982 Site Visit Team, NIGMS, University of Arizona, Tucson, Arizona
1985 Site Visit Team and Special Review Committee, NIH, University of Oklahoma, Oklahoma City, Oklahoma
1985 Wayne State University School of Medicine, Representative to 1985 Quinquennial Meeting of U.S. Pharmacopeial Convention
1990 Wayne State University School of Medicine, Representative to 1990 Quinquennial Meeting of U.S. Pharmacopeial Convention
1990-93 Chairman, Sloan Epidemiology Unit Advisory Committee for Boston University Fever Study
1990 FDA Antiviral Drugs Advisory Committee to review AZT for children
1991 NHLBI Working Group on Asthma & Pregnancy
1993-94 NIH Panel for the Consensus Development Conference (CDC) on the Effect of Corticosteroids on Perinatal Outcomes
1994 NICHD/University of Pennsylvania Conference on Neonatal Pain:
Physiology and Management

1994 American Society of Hospital Pharmaceuticals Workshop on Prescribing Errors

1995 FDA/NIH Workshop on Psychopharmacology in Children & Adolescents

1996 Chair, Section on Pediatric and Perinatal Pharmacology, American Society for Clinical Pharmacology and Therapeutics

1996-2000 Board of Directors, American Society for Clinical Pharmacology and Therapeutics

1996 International Life Sciences Institute Working Group on Research Strategy for Age-Related Differences in Susceptibility

1996 40th Nestle Nutrition Workshop on “Clinical Trials in Infant Nutrition”

1996- United States Pharmacopeia Pediatrics Advisory Panel

1997-99 Chair, Section on Pediatric and Perinatal Pharmacology, American Society for Clinical Pharmacology and Therapeutics

1997-2000 Publication Committee, American Society for Clinical Pharmacology and Therapeutics

1997-2000 Membership Committee, American Society for Clinical Pharmacology and Therapeutics

2000 NIH Cardiovascular Sciences Review Group ZRG1 PHRA (01) Special Emphasis Panel (Review of Pharmacogenetics Network Applications)

2000 FDA Pediatrics Advisory Committee

2000 - 05 Member, American Board of Clinical Pharmacology (Specialty Exam Board); Member of Examination Committee

2002 - 2004 Vice Chair and Chair-elect, American Board of Clinical Pharmacology

2002 - Chair, Data Safety Monitoring Board, Levofloxacin Pediatric National Study, Johnson & Johnson Pharmaceutical Research and Development

2002 - 07 Data Safety Monitoring Board, NICHD PRIDE Study

2002 Chair, NICHD Expert Panel, BPCA Priority Off Patent Drug List

2002 Medicine and Pharmaceuticals Working Group, NICHD National
Children’s Study

2004-2006  President, American Board of Clinical Pharmacology
2005-2010  National Institute of Child Health and Human Development National
           Advisory Council

STATE AND LOCAL BOARDS AND COMMITTEES

1974-79  Executive Committee, Kansas Chapter American Academy of Pediatrics
1975-79  Pediatric Representative on University of Kansas, Medical Center
         Poison Control and Pharmacy, Therapeutics Committee
1976-79  Secretary-Treasurer, Kansas Chapter American Academy of Pediatrics
1979    Quality Assurance Committee, University of Kansas Medical Center
1979    Utilization Review Committee, University of Kansas Medical Center
1979    Pediatric Department Chairman Search Committee, University of
         Kansas Medical Center
1980-    Pharmacy and Therapeutics Committee, Children’s Hospital of
         Michigan
1981-    Chairman, Pharmacy and Therapeutics Committee, Children’s Hospital of
         Michigan
1980-83  Antibiotic Utilization Review Committee, Children’s Hospital of
         Michigan
1980-84  Pediatric Chairman’s Senior Advisory Committee, Wayne State
         University School of Medicine
1980-83  Pediatric Faculty Housestaff Committee, Children’s Hospital of
         Michigan
1980-95  Pediatric Department Education Committee, Wayne State University
         School of Medicine
1980-95  Promotions and Tenure Committee, Department of Pediatrics, Wayne
         State University School of Medicine
1981-95  Human Investigations Committee, Children’s Hospital of Michigan
1981-82  Personnel Committee, Board of Directors, Children’s Hospital of
         Michigan
1982-95  Year IV Medical Student Curriculum Committee, Wayne State University School of Medicine
1985-91  Chairman, Drug Utilization Subcommittee, Children’s Hospital of Michigan
1983-85  Promotions and Tenure Committee, Wayne State University School of Medicine
1983-86  Executive Committee, Faculty Senate, Wayne State University School of Medicine
1983-84  Department of Pediatrics Advisory Committee on Fellowship Training and Research
1983-84  Steering Committee of the Medical Staff, Children’s Hospital of Michigan
1983-85  Finance Committee, Board of Directors, Children’s Hospital of Michigan
1985-91  Children’s Hospital of Michigan Research, Advisory Committee
1987-95  Medical Executive Committee, Children’s Hospital of Michigan
1987-90  University Council, Wayne State University
1987-90  Finance Committee of the University Council, Wayne State University
1989-90  Promotion and Tenure Advisory Committee to the Provost, Wayne State University
1992-95  Mott Center Human Growth & Development Steering Committee, Wayne State University
2001    Chair, UHS External Advisory Committee.
2002-03  UMKC Millenium Committee
2000-2001 UMKC-SOM Committee for Evaluation of Missouri Endowed Chairs
1995-    Children’s Mercy Hospital Research Council
1996 -   Children’s Mercy Hospital Joint Conference Committee of the Central Governing Board
1995 - Children’s Mercy Hospital Department Chairman’s Council
1999 - Children’s Mercy Hospital Quality Council
1999-2002 KSALSI Focus Area Advisory Committee
2002 - 06 KSALSI Institutional Advisory Committee

GRANT SUPPORT

1993-95 Task Force on Environmental Programs, Wayne State University
1970-75 NIH/GMS Placental Transfer of Drugs $120,000
1970-72 PMAF, Beginning Investigator Award 5,000
1972-74 Ciba Geigy, Study of Stimulant Medication in Hyperactive Children 5,000
1972-74 Upjohn Company, Pharmacokinetics of Dicloxacillin 20,000
1972-74 PMAF, Beginning Investigator Award 5,000
1973-74 Intramural Grant, Study of Stimulant Medication in Hyperactive Children 5,000
1974-77 Syntex Research, Analgesic Effects and Pharmacokinetics of Naproxen in Children 60,000
1974-76 PMAF, Career Development Award 60,000
1975-79 NIH/GMS Breast Milk Excretion of Drugs 120,000
1979-80 Faigle Foundation, Theophylline Clearance in Cystic Fibrosis Patients 5,000
1980-81 Park-Davis, Chloramphenicol in Children 15,000
1980-81 Park-Davis, Vidarabine Pharmacokinetics in Infants 25,000
1981-84 Faigle Foundation, D-Penicillamine for Treatment of BPD 33,000
1981-82 Lederle, Piperacillin Pharmacokinetics in Children 7,500
1981-83 Merrill-Dow, Chloramphenicol in Children 5,000
<table>
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<tr>
<th>Year</th>
<th>Sponsor</th>
<th>Project Description</th>
<th>Funding Amount</th>
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<tr>
<td>1982-83</td>
<td>Eli Lilly Company</td>
<td>Moxalactam CSF Diffusion</td>
<td>12,000</td>
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<td>1982-83</td>
<td>Hoffman LaRoche</td>
<td>Ceftriaxone CSF Diffusion</td>
<td>5,000</td>
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<tr>
<td>1982</td>
<td>Faigle Foundation</td>
<td>Aspirin Metabolism in Children with Reye Syndrome</td>
<td>10,000</td>
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<tr>
<td>1983-85</td>
<td>Boots Laboratories</td>
<td>Antipyretic Effect and Pharmacokinetics of Ibuprofen</td>
<td>65,000</td>
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<td>1983-85</td>
<td>Skillman Foundation</td>
<td>Adverse Drug Reaction Monitoring</td>
<td>165,000</td>
</tr>
<tr>
<td>1985-87</td>
<td>Faigle Foundation</td>
<td>Neoptrin Excretion as an Indicator of Transplant Rejection</td>
<td>15,000</td>
</tr>
<tr>
<td>1985-87</td>
<td>Tennis and Crumpets</td>
<td>Therapeutic Drug Monitoring</td>
<td>125,000</td>
</tr>
<tr>
<td>1987-89</td>
<td>McNeil Laboratories</td>
<td>Antipyretic Effect and Pharmacokinetics of Ibuprofen</td>
<td>67,243</td>
</tr>
<tr>
<td>1991-92</td>
<td>Burroughs-Wellcome Visiting Professorship Award</td>
<td>Dr. Richard Weinshilboum, Visiting Professor</td>
<td>1,850</td>
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<tr>
<td>1992-94</td>
<td>McNeil Laboratories</td>
<td>Clinical Pharmacology Fellowship Award</td>
<td>15,000</td>
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<tr>
<td>1992</td>
<td>Innovative Technology</td>
<td>for Measurement of Lead in Blood, Center for Disease Control Approved but not funded</td>
<td>190,080</td>
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<tr>
<td>1992</td>
<td>WSU Research Stimulation Grant</td>
<td>Development of Portable Assay for Blood Lead</td>
<td>3,000</td>
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<tr>
<td>1992-93</td>
<td>Providing Clinical Information on Hospital Wards</td>
<td>National Library of Medicine, Michele Klein, P.I.</td>
<td>331,010</td>
</tr>
<tr>
<td>1992-93</td>
<td>Pfizer Visiting Professorship Award</td>
<td>Dr. Jacob Aranda, Visiting Professor</td>
<td>6,000</td>
</tr>
<tr>
<td>1993-94</td>
<td>The use of opiates for the treatment of children with severe pain, Ronald McDonald Children’s Charities; Dr. Lieh-Lai, P.I.</td>
<td></td>
<td>50,000</td>
</tr>
<tr>
<td>1993</td>
<td>WSU Supplemental Research Equipment Fund</td>
<td>R. Kauffman &amp; Y. Ravindranath, Co-P.I.s</td>
<td>18,430</td>
</tr>
</tbody>
</table>
1994-95  NIEHS Environmental Toxicology Center Grant,  
       WSU Institute of Chemical Toxicology 
       Investigator & Human Core Co-Director, Dr. Ralph Kauffman 

1994-99  Network of Pediatric Pharmacology Research Units 
       National Institute of Child Health and Human 
       Development, Principal Investigator 

1994  “Fighting Medication Errors” Seminar, 6/94 
       Glaxo Inc., Dr. Ralph Kauffman, Activity Director 

1994  “Fighting Medication Errors” Seminar, 6/94 
       Baxter Biotech-Hyland 

1994  “Fighting Medication Errors” Seminar, 6/94 
       Miles Inc/Biological Products 

1997  Bristol-Myers Squibb, Treatment of Children with 
       ADHD, Principal Investigator 

1997  Bristol-Myers Squibb, Treatment of Children with 
       ADHD, Principal Investigator 

1997  Hoechst-Marion Roussel 

1999-2004  Network of Pediatric Pharmacology Research Units 
           National Institute of Child Health and Human 
           Development, Principal Investigator 1999-2000, Program 

2004-2005  Network of Pediatric Pharmacology Research Units 
           National Institute of Child Health and Human 
           Development, Program Director. (Retired from grant in 
           2005) 

PUBLICATIONS

Original Observations in Refereed Journals


29. Bowman DB, Aravind MK, Miceli JN, Kauffman RE: Reversed-phase high performance liquid chromatographic method to determine ceftriaxone in biological


41. Tolia V, Calhoun JA, Kuhns LR, Kauffman RE: Lack of correlation between
extended pH monitoring and scintigraphy in the evaluation of infants with

42. Tolia V, Kauffman RE: Comparison of evaluation of gastroesophageal reflux in
infants using different feedings during intraesophageal pH monitoring. J Ped

43. Meert KL, Kauffman RE, Deshmukh DR, Sarnaik AP: Impaired oxidative
metabolism of salicylate in Reye’s Syndrome. Dev Pharmacol Therap, 15:57-60,

44. Tolia V, Brennan S, Aravind MK, Kauffman RE: Pharmacokinetic and
pharmacodynamic study of midazolam in children during

45. Rosenberg NM, Meert KL, Yee H, Kauffman RE: Occult cocaine exposure in

46. Kauffman RE, Sawyer LA, Scheinbaum ML: Comparison of antipyretic efficacy

47. Kauffman RE, Nelson MV: Effect of age on ibuprofen pharmacokinetics and

48. Tolia V, Kuhns L, Kauffman R: Correlation of gastric emptying at one and two

49. Tolia V, Kuhns L, Kauffman RE: Comparison of simultaneous esophageal pH
monitoring and scintigraphy in infants with gastroesophageal reflux. Am J

50. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal
Maturation on Perinatal Outcomes: Effect of corticosteroids for fetal maturation

51. Rosenberg NM, Meert KL, Marino D, Yee H, and Kauffman RE: Occult Cocaine
and opiate exposure in children and associated physical findings. Pediatr

52. Rosenberg NM, Marino D, Meert K, Kauffman RE: Comparison of Cocaine and
Opiate Exposures Between Young Urban and Suburban Children. Arch Pediatr

Collection by Paper for Lead Analysis by Graphite Furnace Atomic Absorption


59. Klein MS; Eames CH; Simpson PM; Szof CA; Humes RA; Kauffman RE. Information at the Point of Care: Effect on Patient Care and Resource Consumption. JHIM 13(1):67-81, 1999.


**Review Articles**


Ralph E. Kauffman, M.D.
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Books and Chapters


Case Reports


Educational Material


Commentaries


Commentaries (Co-authored with American Academy of Pediatrics’ Committee on Drugs)


Other Published Materials


Book Reviews


PUBLISHED ABSTRACTS


46. Rosenberg NM, Meert KL, Marino DK, Yee H, Kauffman RE: Occult cocaine


PRESENTATIONS


Fifth Annual Meeting and Continuing Education Conference, Minnesota Society of Hospital Pharmacists, Minneapolis, Minnesota. April 16, 1982.


26. Kauffman RE: Special considerations for administering intravenous antibiotics to pediatric patients. Presented at Symposium on Management of Common Pediatric Infectious Diseases, Children’s Hospital of Michigan, Wayne State University, Detroit, Michigan, September 13, 1983.


82. Kauffman, RE. Recent Regulatory Changes in Pediatric Drug Development: Implications for Academic Medical Centers, Visiting Professor, Cincinnati Children's Hospital, Cincinnati, OH, Oct 15, 1998.

83. Kauffman, RE. Influence of Childhood Development on Drug Metabolism. Pfizer Visiting Professor Lecture, University of Utah, Primary Children's Hospital, Salt Lake City, UT, Jan 20, 1999.

84. Kauffman, RE. Recent Changes in Drug Development for Children: Implications for Academic Medical Centers. Pfizer Visiting Professor lecture, Primary Children's Hospital, University of Utah, Salt Lake City, UT, Jan 21, 1999.


89. Kauffman, RE. New Developments in Pediatric Drug Research: Recent Initiatives and Implications for Pediatricians. American Academy of Pediatrics Committee on Pediatric Research, Rosemont, IL, April 9, 1999.

91. Kauffman, RE. Overview of Drug Metabolism during the First Year of Life. William Evans Memorial Lecture, Children's Hospital of Michigan, Wayne State University, Detroit, MI, May 19, 1999.


103. Kauffman, R.E. Psychoactive Drug Therapy for Children: Perspectives, Problems


