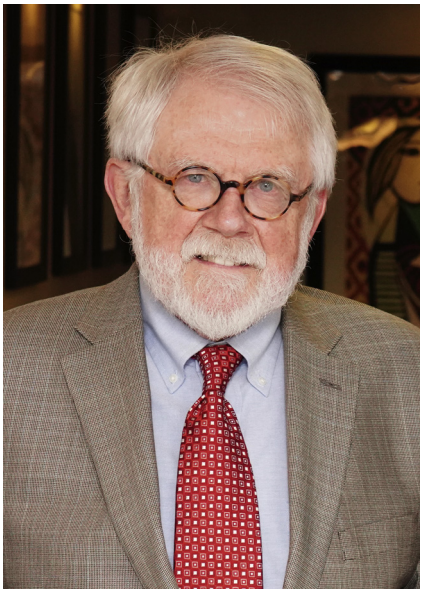
Giants in Obstetrics and Gynecology Series: A profile of James M. Roberts, MD

Roberto Romero, MD, DMedSci, Editor-in-Chief for Obstetrics

Dr James Roberts has made seminal contributions to the understanding of the physiology of pregnancy and, in particular, to the mechanisms of disease responsible for preeclampsia. His research includes endothelial cell dysfunction, oxidative stress, and other factors that play a role in the pathogenesis of preeclampsia; the use of antioxidant therapy to prevent the syndrome; identification of clinical subtypes of preeclampsia; and assessment of the long-term cardiovascular risk of the disorder. Dr Roberts is currently an investigator at the Magee-Womens Research Institute and a Professor of Obstetrics Gynecology and Reproductive Sciences, Endocrinology, and Clinical and Translational Medicine at the University of Pittsburgh. He was the founding Director of the Magee-Womens Research Institute and formerly the Elsie Hilliard Hillman Chair in Women's and Infants' Health Research at the University of Pittsburgh. For his many original contributions to the understanding of preeclampsia and other obstetrical syndromes, Dr Roberts is herein recognized as a "Giant in Obstetrics and Gynecology".



Dr James M. Roberts

The Path To Medicine

The second of four children, Jim was born in 1941 and raised in a blue-collar household in Taylor, Michigan. His father, originally from Pennsylvania, moved to the Detroit area during the Great Depression to work at the Ford Motor Company, first as a timekeeper, then as an accountant.

Jim envisioned a college education, the first member of his family to follow an academic path. To make this dream possible, he entered a scholarship competition sponsored by Ford, for which he had to submit an essay about what he would do with his degree. "I wrote that I wanted to be a physician, because that's the only thing I knew people did after attending college," he said.

The recipient of this four-year scholarship, Jim began his undergraduate journey in 1959 at the University of Michigan in Ann Arbor, Michigan, where he would spend his next 12 years. When I asked Jim about his decision to go into obstetrics and gynecology, he replied, "it was fate." Recognizing that the Ford scholarship would not fully cover medical school, he sought other financial aid options. This brought him into contact with Dr John Gosling, the Dean overseeing student loans at the University of Michigan, who happened to be an obstetrician and gynecologist.

Dr. Gosling offered Jim the opportunity to see patients with him and involved him in bibliographic research projects, introducing him to the academic side of medicine. Once he began to visit patients with Dr. Gosling, Jim decided "there could not be anything more fun than taking care of patients and being paid to learn." Already enthusiastic about academics, Jim became hooked on obstetrics. Although the field was not necessarily what he had set out to study, he was glad the path opened up for him. He remembers his lifelong mentor and friend as a "remarkable individual, a true character," who delivered Jim's first child.

Residency in Obstetrics and Gynecology at the University of Michigan

During his medical school years at the University of Michigan, Jim worked with Dr Allan Beaudoin, Professor of Anatomy and Cell Biology, investigating teratogenesis and the role of the thyroid gland in embryonic development, which resulted in Jim's first published papers.[1,2] As a resident, he also published on hemorrhagic and endotoxic shock[3] and intrauterine contraceptive devices[4] and conducted research on the placental transfer and metabolism of endogenous steroids.[5] Jim did not enjoy research as a resident, which, it

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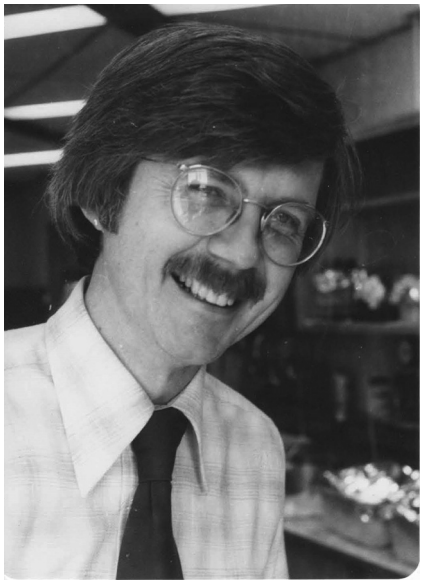
later became clear, was a reaction to the time-consuming constraints of a very busy residency. He recognized the value and importance of investigative experience as part of an academic career; nevertheless, he determined that, when his residency was complete, he would never do research again.

Jim was drafted after graduating from medical school in 1967 and served in the Armed Forces as a Major in the Obstetrics and Gynecology Service for the United States Army Medical Corps. Based at a hospital in Fort Carson, Colorado, he acquired surgical training that cemented his love for patient care, but the experience also made it clear that he wanted to do more than practice medicine. Jim planned to return to an academic career at the University of Michigan, brainstorming ways he could do this without doing research, until fate intervened again.

Dr Robert Jaffe, who Jim knew from the University of Michigan, had accepted a position as Professor and Chair at the University of California, San Francisco (UCSF), and became a member of UCSF's world-renowned Cardiovascular Research Institute (CVRI). Dr Jaffe reached out to encourage Jim to consider a position at the Institute.

Jim enjoyed the "prep school for academicians" environment provided by CVRI, which included small-group teaching, grant and paper writing, and hands-on academic training, and decided it would be a good fit. When Jim met with CVRI Director Dr Julius Comroe, the topic turned to his research project, and he interrupted to say that he did not do research. "Dr Roberts, this is the Cardiovascular *Research* Institute," Dr Comroe said; and so, Jim told me, "I did research. And it turned out to be remarkable." It was soon evident that this was due to Jim's joy of in-depth thinking and problem-solving, for which time was not available as a Resident. "I was about six weeks into my research experience when I fell in love with research and realized it was what I wanted to do."

FIGURE 1
Jim as a new faculty member at University of California, San Francisco



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The First Steps in a Research Career

Jim's first project was entitled "The modification of adrenergic receptors by sex steroids in rabbit myometrium," and he developed a research strategy to mix radioactive drugs with tissue homogenates, thereby identifying the pieces that a given drug bonds to as "receptors." The number of receptors could then be quantified, and correspondent changes could be recorded.[6,7] It was a novel area of investigation at the time, and little was known about the effectiveness of this strategy, either in conducting the study or analyzing the data. However, Jim's mentor, Dr Alan Goldfien, an endocrinologist and a founding member of CVRI, was an expert on catecholamines and adrenergic receptors, which allowed them to avoid several confounders, such as autoxidation.

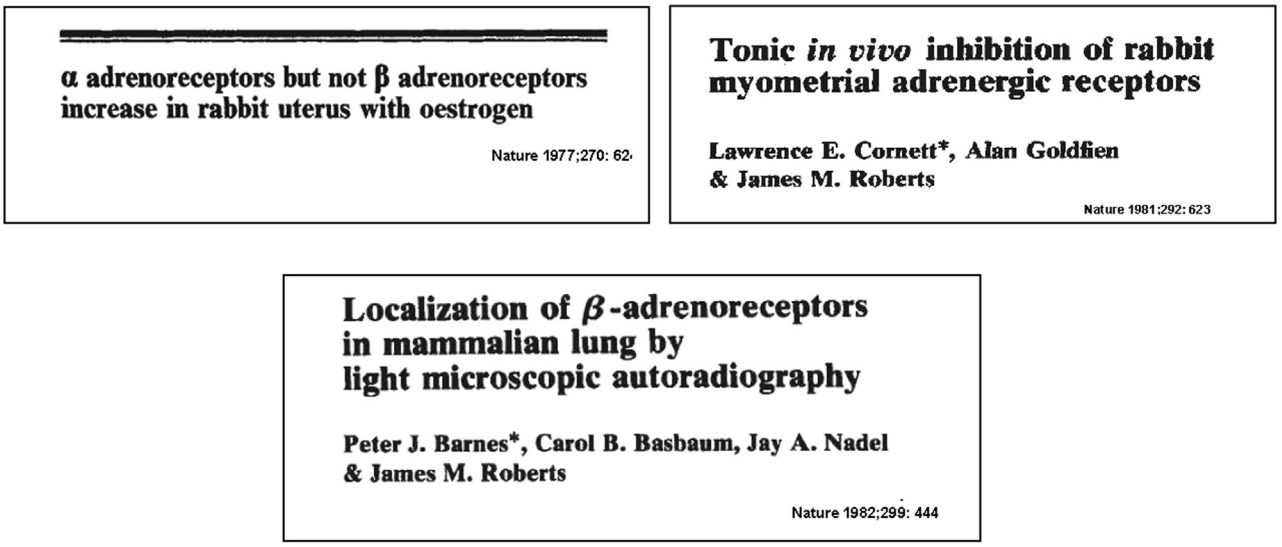
Aiming to relate his efforts to the field of obstetrics and gynecology, Jim began taking the data that were generated by his research on receptor characteristics and analyzing it in terms of the pharmacology of tocolytic agents and managing preterm labor with ritodrine and other beta-adrenergic agents.[8]

Jim was also fortunate to become associated with a new professor at UCSF, Daniel Santi, PhD, who was an expert in the analysis of the interaction of small molecules and proteins. He provided Jim with an in-depth understanding of receptor ligand interactions. This later formed the basis for a graduate course Jim taught, "Obstet Gynecol 231: Quantitation of Biological Responses: Principles of Mass Action," which was a requirement for a pharmacology or endocrinology doctorate.

Jim completed his fellowship and accepted a position with the Department of Obstetrics, Gynecology and Reproductive Sciences at UCSF, where he continued to work with Dr Goldfien on adrenergic receptors (Figure 1). Dr Robert Lefkowitz, Professor of Medicine and Biochemistry at Duke University School of Medicine, heard Dr Goldfien speaking about his work with Jim on the possible modifications of adrenergic receptors by sex steroids. Dr Lefkowitz found the topic fascinating and began to work on the topic in his own, much larger, laboratory. The two groups became competitors in the race to identify adrenoceptor binding sites within the uterus. Jim published his article in *Nature*[9] first, followed closely by Dr Lefkowitz's publication in the *Journal of Clinical Investigation*. The two became respected associates, and Dr Lefkowitz later wrote a promotion letter for Jim. Dr Lefkowitz went on to be awarded the 2012 Nobel Prize in Chemistry for his work on G-protein-coupled receptors.

After publication, Jim was able to secure more funding, including two National Institutes of Health grants, that enabled him to hire postdoctoral Fellows and enlarge his

FIGURE 2
Papers published in *Nature* on adrenergic receptors


α adrenoreceptors but not β adrenoreceptors increase in rabbit uterus with oestrogen

Nature 1977;270: 62

Tonic *in vivo* inhibition of rabbit myometrial adrenergic receptors

Lawrence E. Cornett*, Alan Goldfien & James M. Roberts

Nature 1981;292: 623

Localization of β-adrenoreceptors in mammalian lung by light microscopic autoradiography

Peter J. Barnes*, Carol B. Basbaum, Jay A. Nadel & James M. Roberts

Nature 1982;299: 444

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research operation. Over the next nine years, he published three more papers in the top science journal *Nature*[10–12] and four articles in the *American Journal of Obstetrics and Gynecology* (AJOG)[13–16] that examined different aspects of adrenergic receptor biology (Figure 2). This was an extraordinary beginning for the career of a physician-scientist.

Jim sought opportunities to focus on research that were more relevant to his specialty. He had developed an interest in preeclampsia after his fellowship in clinical hypertension at CVRI and 10 years on the medicine faculty caring for patients with hypertension and in obstetrics caring for women with hypertensive disorders of pregnancy. When he was approached by Dr Jaffe to be a project leader of a Program Project Grant, a funding source for interdisciplinary research in academic medicine that merges basic science and clinical work, Jim found the prospect intriguing. He gladly took on the challenge and submitted a successful Program Project Grant that ran for over 20 years and produced more than 100 peer-reviewed publications, contributing significantly to the understanding of preeclampsia.

His new role as PI and leader of the Program Project Grant allowed Jim to establish relationships with many great scientists at UCSF, such as Dr Susan Fisher and Dr Robert Taylor, and collaborations all over the country. In his preparations for the Program Project Grant, Jim worked with preeclampsia experts to identify the important questions about the disorder. Subsequently, he organized weekly meetings with experts who specialized in areas relevant to those questions, but who had no prior interest in and little knowledge of preeclampsia.

"It was a fascinating experience," Jim recalled. "The experts offered completely different views on the issues around preeclampsia than anybody working in that dedicated space. Many of the researchers involved in the Program Project Grant had thought about the syndrome in one particular way for a long time. With the interdisciplinary collaboration, they began to look at the disorder in a very different manner. It was through this process that the focus on endothelial dysfunction emerged and matured." The power of this interactive approach strongly influenced Jim's research strategy and future career choices.

Endothelial Dysfunction in Preeclampsia

Some of Jim's most pioneering work began with the interactions of the Program Project Grant. One of the experts included in the conversations was interested in the endothelium, which Jim had always regarded as a simple blood vessel coating. However, as he learned more about endothelial functions and how the tissue blunts responses to pressor agents, prevents coagulation by modifying platelet function, and maintains fluid within blood vessels, he realized what a sophisticated and important tissue it really is. It struck Jim that it was these very functions that became deranged in preeclampsia. Indeed, women with preeclampsia have an exaggerated response to pressor agents and platelet activation and are in a hypercoagulable state. In addition, they have a loss of fluid from the intravascular space, which is responsible for edema. He also noted the profound changes in endothelial morphology in glomeruloendotheliosis, a lesion considered quite characteristic of preeclampsia.

Based on this body of evidence, Jim proposed a theory: when the placenta is not adequately perfused, it produces substances in response to ischemia that damage the endothelium of the maternal blood vessels. He discussed this theory with several colleagues and described the conversations as "an unusual experience, because they acted as if they

FIGURE 3
Endothelial cell injury leads to development of preeclampsia

Preeclampsia: An endothelial cell disorder

James M. Roberts, MD, Robert N. Taylor, MD, PhD, Thomas j. Musci, MD,
George M. Rodgers, MD, PhD, Carl A. Hubel, PhD, and Margaret K. McLaughlin, PhD
San Francisco, California

Despite intense study preeclampsia remains enigmatic and a major cause of maternal and fetal morbidity and mortality. Most investigative efforts have focused on the hypertensive component of this disorder with reduced attention given to other equally important characteristics. Increased sensitivity to pressor agents and activation of the coagulation cascade occur early in the course of preeclampsia, often antedating clinically recognizable disease. Inasmuch as endothelial cell injury reduces the synthesis of vasorelaxing agents, increases the production of vasoconstrictors, impairs synthesis of endogenous anticoagulants, and increases procoagulant production, these cells are likely to be implicated in the pathophysiology of preeclampsia. Indeed, evidence of endothelial cell injury is provided by the most characteristic morphologic lesion of preeclampsia, glomerular endotheliosis. Additional support for this hypothesis is derived from reports that indicate increased levels of circulating fibronectin (which can be released from injured endothelial cells) and increased factor VIII antigen present in the blood of preeclamptic women. More recently, direct evidence of activities that injure endothelial cells in vitro and increase the contractile sensitivity of isolated vessels has been presented. We propose that poorly perfused placental tissue releases a factor(s) into the systemic circulation that injures endothelial cells. The changes initiated by endothelial cell injury set in motion a dysfunctional cascade of coagulation, vasoconstriction, and intravascular fluid redistribution that results in the clinical syndrome of preeclampsia.
(AM J OBSTET GYNECOL. 1989;161:1200-4.)

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had known it their entire lives. And yet, when I looked at the Index Medicus [the precursor to MEDLINE that provided an index to biomedical journal articles[17]], there was no place where 'endothelium' showed up with 'preeclampsia.' It was the kind of thing that was such a very sensible idea that people felt they had always known it."

Jim knew that it was important that he organize the concept and arguments in favor of preeclampsia as an endothelial cell disorder and produced the only hypothesis paper of his career: "Preeclampsia: an endothelial cell disorder,"[18] which was published in *AJOG* in 1989 (Figure 3). Jim said that paper was "a real pleasure to write because the whole concept just made so much sense." The paper became a "citation classic," with >1480 citations to date and was recognized as a top-cited paper in obstetrics and gynecology by *AJOG* in 2009.[19]

The next step was to look for substances in maternal blood of women with preeclampsia that could injure endothelial cells. For these experiments, Jim collaborated with Dr Robert Taylor, who was completing a fellowship at UCSF and was beginning research on growth factors. They preloaded endothelial cells in vitro with chromium and exposed them to diluted serum samples from women with and without preeclampsia. They found that the cells that were exposed to serum from women with preeclampsia, but not from normal pregnancies, leaked chromium, which indicated endothelial cell damage.[20] They then exposed endothelial cells to serum of normal women and those with preeclampsia and analyzed several consequences of this,[21] which led to the partial characterization of mitogenic activity of preeclampsia on smooth muscle that they termed "Endogenous Ligand conferring MitogEnic Response."[22]

After testing endothelial function and establishing that there was endothelial cell dysfunction before and during clinical preeclampsia, Jim and his group undertook an effort to identify soluble factors that were responsible for the disorder. It was a difficult task. Jim concluded that the evidence in favor of endothelial cell dysfunction was compelling, but technologic developments were required to identify the soluble factors responsible for the abnormal endothelial cell function in the syndrome.

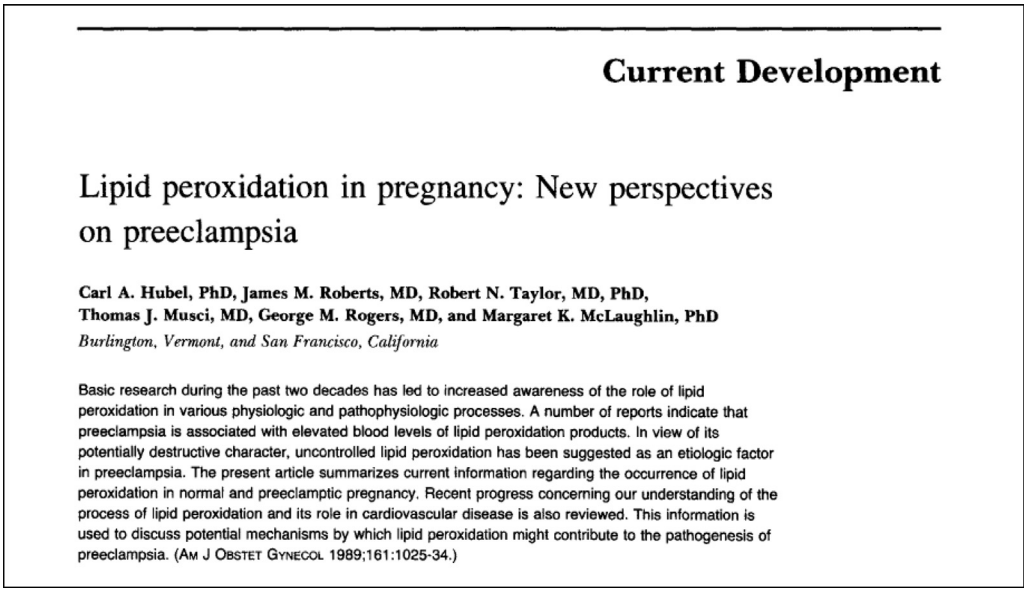
Jim told me that one of the best biomarkers of endothelial cell dysfunction is the plasma concentration of cellular fibronectin.[23,24] He also credited Dr C.D. Hsu with having identified thrombomodulin as a marker for endothelial cell dysfunction in preeclampsia.[25,26] However, Jim quickly remarked that, although these markers are elevated in patients with preeclampsia, cellular fibronectin (or any other biomarkers) identified only a subset of patients who were at risk for preeclampsia.

This observation underscores another point that Jim has made frequently; namely, that one reason researchers have had trouble looking for predictors and preventive agents for preeclampsia is that it is very unlikely to be just one disease.[27]

The Link Between Placental Ischemia and Endothelial Dysfunction

In the 1980s, Jim became aware of the work of graduate student Carl A. Hubel, who was working with Dr Margaret McLaughlin at the University of Vermont. Carl proposed that

FIGURE 4
Lipid peroxidation is an etiologic factor that contributes to the pathogenesis of preeclampsia



Current Development

Lipid peroxidation in pregnancy: New perspectives on preeclampsia

Carl A. Hubel, PhD, James M. Roberts, MD, Robert N. Taylor, MD, PhD, Thomas J. Musci, MD, George M. Rogers, MD, and Margaret K. McLaughlin, PhD
Burlington, Vermont, and San Francisco, California

Basic research during the past two decades has led to increased awareness of the role of lipid peroxidation in various physiologic and pathophysiologic processes. A number of reports indicate that preeclampsia is associated with elevated blood levels of lipid peroxidation products. In view of its potentially destructive character, uncontrolled lipid peroxidation has been suggested as an etiologic factor in preeclampsia. The present article summarizes current information regarding the occurrence of lipid peroxidation in normal and preeclamptic pregnancy. Recent progress concerning our understanding of the process of lipid peroxidation and its role in cardiovascular disease is also reviewed. This information is used to discuss potential mechanisms by which lipid peroxidation might contribute to the pathogenesis of preeclampsia. (Am J Obstet Gynecol 1989;161:1025-34.)

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oxidative stress could alter vascular function and found that pressor responses to angiotensin could be increased and endothelial depressor responses inhibited by inducing oxidative stress in rats,[28] which suggested that the reactive oxygen species might be the link between the placenta endothelium.[29]

"Oxidative stress is a nasty pathologic process that damages tissues and is self-perpetuating and accelerating, presenting the same features as preeclampsia does clinically," Jim said. "The presence of oxidative stress in serum, tissues, and placenta provides some of the strongest evidence available for understanding the pathophysiology of preeclampsia."

Carl and Jim's paper about the role of oxidative stress in preeclampsia was published in *AJOG* and became another citation classic that has been cited more than 430 times to date (Figure 4). This interaction resulted in a long and fruitful working relationship between Carl and Jim, beginning with postdoc training and progressing to Carl's leadership of the group Jim began in the 1980s.

Parallels Between Preeclampsia and Atherosclerosis

Jim told me that there are many parallels between atherosclerosis and preeclampsia; changes in endothelial function and intravascular inflammation in atherosclerosis are also features present in preeclampsia. One of the most striking similarities is the presence of atherosis, a lesion that is seen in the spiral arteries of a subset of women with preeclampsia.

These lesions, also present in other disorders, "look for all the world like an atherosclerotic plaque that would be seen in a systemic vessel," he said. For many years, the parallel between atherosclerosis and preeclampsia guided much of the research that Jim and his colleagues conducted that used atherosclerosis to learn more about preeclampsia. Now, he says, "I am excited because the research is going in the other direction, looking at what preeclampsia can teach us about atherosclerosis. It is an area and an approach that, I think, have some real potential payoffs." Dr Hubel now leads an American Heart Association program testing these relationships.

Magee-Womens Research Institute at the University of Pittsburgh

In 1992, Jim was recruited by Dr Richard Sweet and the leadership at the University of Pittsburgh to launch a women's health research institute at the Magee-Womens Hospital in Pittsburgh, Pennsylvania. Ms Irma Goertzen, who came from an academic center at the University of Washington to be CEO of Magee-Womens Hospital, had the vision to establish an institute devoted to research in women's health. Jim's ability to emphasize interactions among those with different backgrounds was a major factor in his decision to make the move to Pittsburgh. Jim also believes that academicians owe it to their specialty to put in administrative time at some point in their careers, and this was the perfect moment for him to do so. Thus, when the Magee-Womens Research Institute (MWRI) was established, Jim served not only as Director, but also as an Investigator. Jim described this as one of the most exciting experiences in his career from day one (Figure 5).

Jim embarked on this new enterprise and was a quick study, gaining respect for his clinical and basic research work. His position at MWRI was self-revelatory, showing Jim

FIGURE 5
University of Pittsburgh's Magee-Womens Hospital, Maternal Fetal Medicine Division (1993)

Back row, left to right: Bill Cromleholme, Jose Prieto, Jim Roberts, Ian Grable, Steve Caritis, Phil Heine, Margaret McLaughlin, Steve Sladek. Front row, left to right: Dan Edlestone, Jye Ping Chiao, Phil Rauk, Lynn Hill, Peg Watt-Morse, Kim Heller, Steve Laifer, Andrea Westerhausen-Larsen.

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strengths he had never fully appreciated. This insight allowed him to cultivate the skills needed to lead a group of investigators successfully and to accomplish tasks effectively, opening up the possibility for other opportunities that he never would have considered based on previous experience.

Another defining experience was his role as Chair of the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network from 1991−1999. In this role, Jim learned the challenges of clinical research. "It's one thing to be putting cells in a dish; it's another thing to have 10,000 women that you're exposing to some treatment that you're hoping is going to be effective, and, when you're three weeks into the project, you realize you wish you had done something different," he mused.

Managing a randomized clinical trial is a demanding undertaking that requires a lot of knowledge before one is prepared to tackle its complexities. When is enough knowledge gained from basic science to justify a clinical trial? Jim replied, "When it works." He further explained, "If the trial doesn't work, everyone always concludes you never had enough information. It is a tremendous accomplishment to make one randomized clinical trial work."

By the late 1990s, the Magee-Womens Research Institute had attracted nearly 100 investigators and had become the number one Obstetrics and Gynecology Research Program funded by the National Institutes of Health Extramural Program, which it remains to this day. Jim said that one of his greatest satisfactions came after he stepped down as Director of MWRI in 2007 and handed the helm over to Dr Yoel Sadovsky, a prominent physician-scientist. "I enjoy seeing the Institute continue to grow, with new investigators, new topics, new strategies, and a new building, but not in the 'Jim Roberts' way' anymore," he shared. "Watching it evolve under Dr Sadovsky has been really great."

Many fruitful collaborations emerged from the work done at the MWRI. For example, Dr Kirk Conrad, a Systems Physiologist, worked from 1994−1999 in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh and the MWRI. He brought considerable expertise in kidney physiology,[30] nitric oxide, and systems biology[31] to the understanding of preeclampsia and the physiology of pregnancy. Dr Conrad has now generated evidence about the important role of the decidua in the pathogenesis of preeclampsia.[32,33] Jim treasures the years

working with Kirk and considers him the ultimate example of the organized, logical, innovative, and persistent investigator (Figure 6).

The Combined Antioxidant and Preeclampsia Prediction Studies

In 1999, Jim was asked to head a trial on the prevention of preeclampsia: the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development on "Antioxidants to Prevent Preeclampsia." The trial was the outcome of a workshop chaired by Jim and presented by the National Heart, Lung, and Blood Institute, which helped to fund the trial.

Jim regarded the trial, known as the Combined Antioxidant and Preeclampsia Prediction Studies, as the chance of a lifetime. He and his team had proposed a hypothesis rationalizing the use of Vitamins C and E to treat preeclampsia and then had the opportunity to direct a randomized, multicenter, clinical trial to assess the benefits.[34] The trial was the logical extension of the ideas formulated by Jim and Drs Hubel, Taylor, and McLaughlin 10 years earlier. "And it didn't work at all," Jim recalled.

Jim said that this trial was the basis for the recommendation of the American College of Obstetricians and Gynecologists (ACOG) not to use Vitamins C and E to prevent preeclampsia. "I don't know why the vitamins didn't work," he said. "I don't think it's appropriate to say that antioxidants across the board don't work. It is accurate that Vitamin C and Vitamin E, given at the time they were given, in the doses they were given, and the forms they were given in, did not work. And there is always the possibility that we chose the wrong antioxidants."

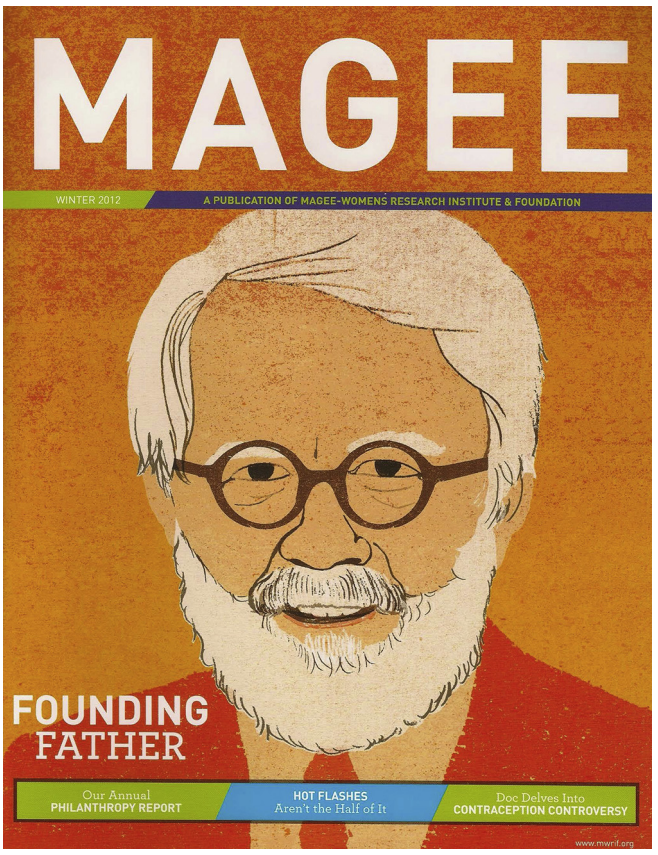
There is more evidence now that indicates that ascorbic acid can act as a prooxidant, and Jim suggested it could be that the type of Vitamin E used in the trial actually interfered with the synthesis of a more beneficial kind of Vitamin E. This idea has not yet been tested.

The Global Pregnancy Collaboration

In 2010, the Bill and Melinda Gates Foundation established a large program to study preeclampsia in low- and middle-income countries, headed by Dr Peter von Dadelszen, who is now at King's College in London. Dr von Dadelszen invited Jim to join the program as a senior advisor and to direct a component of the grant, The Global Pregnancy Collaboration (CoLab).[35]

CoLab originally was intended to bring together groups from around the world to share data and biologic materials, which was an approach new to reproductive research but very successful in oncology and cardiology. Recently, CoLab's 34 centers have expanded their scope to facilitate worldwide collaboration through position papers,[36,37] standardization of data and sample acquisition,[38] and the preparation of a harmonized database available to investigators worldwide.[39] The Collaboration supports training, through the EMPOWER training program and the development of consortia in low-resource settings, such as Latin America and Indonesia.

FIGURE 6
Cover of *MAGEE: A Publication of Magee-Womens Research Institute & Foundation*, Winter 2012



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In 2014, the Preeclampsia Foundation's Preeclampsia Registry was accepted into CoLab. The Registry, launched in 2013, is an effort to initiate a "living biobank" of those women affected by preeclampsia and their family members and researchers to advance knowledge, disease prevention, and treatment. Jim has served on the Foundation's Scientific Advisory Board since 2000 and as a co-chair for the Registry's Scientific Advisory Board since 2012. Most recently, Jim and Dr Leslie Myatt, from Oregon Health & Sciences University, chaired a National Heart, Lung, and Blood Institute/NICHD workshop to recommend research strategies for preeclampsia.[40]

The Story Behind Changing the Requirement for Proteinuria to Diagnose Preeclampsia

When Dr James Martin, Chief of Maternal-Fetal Medicine and Director of the Center for Maternal and Fetal Care at the University of Mississippi, became President of ACOG in 2011, he asked Jim to chair a newly created task force on hypertension in pregnancy. Grateful for this opportunity, Jim embarked on his tenure as Chair with the idea of identifying areas in which the care of pregnant women could be

improved. He also saw this as an opportunity to explore the characterization of preeclampsia as more than hypertension and proteinuria.

These two goals converged because the group used data from an in-depth assessment of maternal deaths by the California Maternal Quality Care Collaborative to determine the current causes of maternal death in preeclampsia. The study revealed that a number of women who had severe preeclampsia, but no proteinuria, had died and that their diagnoses had not included preeclampsia.[41] This led the ACOG task force to recommend that hypertension in pregnancy that is accompanied by other systemic findings other than proteinuria be considered and managed as preeclampsia.

Other areas of importance that were addressed by the task force were the detection and management of postpartum preeclampsia and increasing patient education on the signs and symptoms of preeclampsia, including in the postpartum period. Jim introduced the evidence-based evaluation tool GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) and included patient representatives in ACOG processes, stressing the importance of education for patients and providers.[42]

Professional Endeavors and Awards

In the late 1980s, Jim, Dr Robert Taylor, and Dr Chris Redman created a meeting format modeled on the prestigious Gordon Research Conferences and called it "Tox Talks." It is an invitation-only gathering that meets every two years now under the leadership of Dr Robert Powers. "Through these meetings, we've built numerous collaborations and interactions over the years and stimulated new directions for research in preeclampsia," Jim said.

Jim is a peer reviewer for 20 journals, including *AJOG*, and currently serves on the editorial board for the *Journal of the Society for Reproductive Investigation*, *Hypertension*, *Women's Health Issues*, and *Reproductive Vascular Medicine: Commentary and analysis on vascular-related disorders in women*.

Jim has received numerous awards from many organizations throughout his career: in 1998, he received the International Society for the Study of Hypertension in Pregnancy Chesley Award for Lifetime Achievement in the study of hypertension in pregnancy; in 2004, NICHD's Duane Alexander Award for Academic Leadership in Perinatal Medicine; in 2008, the Society for Gynecologic Investigation's Frederick Naftolin Award for Mentorship and also the Hope Award for Lifetime Achievement given by the Preeclampsia Research Foundation; in 2011, the Society for Reproductive Investigation's Distinguished Scientist Award; and, in 2017, the DeCherney Lifetime Distinguished Service Award of the Society for Reproductive Investigation. He is a member of the National Academy of Medicine of the United States and has been a Fellow *ad eundem* of the Royal College of Obstetricians and Gynecologists since 2000.

In 2009, Jim was recognized by the Perinatology Research Branch (PRB), NICHD/NIH, in Detroit, Michigan, for his contributions to understanding preeclampsia with a photo upon its Wall of Honor. The PRB also invited Jim to participate in a symposium on preeclampsia in 2018 (Figure 7) and honored him as a distinguished participant in the PRB Lectureship Series with an engraved nameplate.

FIGURE 7

James visits the Perinatology Research Branch of the National Institute of Child Health and Human Development/National Institutes of Health in Detroit, MI, for their Preeclampsia Symposium (October 29, 2018)

Front Row, left to right: Dr. Chaur-Dong Hsu, Dr. Carl A. Hubel, Dr. Kirk P. Conrad, Dr. James Roberts, Dr. Roberto Romero.

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Lasting Impact of Mentors

Jim recognizes a number of important mentors who influenced his career. From the beginning, Dr Gosling taught Jim that academics could be an exciting choice. Dr Russell K. Laros was the "ultimate clinician" at the University of Michigan and taught Jim the art of handling stressful situations. Dr Jaffe, in addition to providing a number of opportunities, inadvertently changed Jim's career path by exposing him to interdisciplinary research through the Program Project Grant.

Dr Donald McNellis, a National Institutes of Health program officer, recruited Jim to lead the NICHD Maternal-Fetal Medicine Units Network, which was an experience that allowed Jim to recognize latent leadership skills. He also recalled exciting intellectual interactions with Dr Robert Taylor, now at the Utah Center for Reproductive Medicine, who possesses an extraordinary sense of humor.

Outside of medicine, Jim credits Eric Hodos, a former US Army Ranger and a skilled cyclist, with teaching Jim that you can always do more than you think you can.

Jim acknowledged Dr Goldfien as the person who had the greatest impact on him, both as a researcher and as a human

being. "Alan was one of the wisest men I'd ever met, someone who could really cut to the important issues," he said. A close, lifelong friendship evolved, and Dr Goldfien served as best man at Jim's wedding.

Additionally, Jim credits the researchers and clinicians he has trained. "People who come in with a different background than you, who look at things differently than you do, keep you in a position where you do not become calcified, locked into one set of ideas" he said. "To me, one of the issues of being a successful academician is to avoid calcification at all costs."

The Future of Preeclampsia Research

Over the course of Jim's career, the results of numerous studies changed conventional thinking about preeclampsia. Today, a better understanding exists concerning maternal-fetal interactions; the two-stage model; a potential mechanistic relationship between preeclampsia and later-life cardiovascular disease; a new appreciation for the link among Vitamin D, preeclampsia, and race; the relationship and potential mechanisms of obesity and preeclampsia; and a clearer concept of preeclampsia subtypes. These advancements have contributed to a broader understanding of preeclampsia and the idea that it is not likely to be just one disease.

"Preeclampsia cannot continue to be approached as one condition defined by a set of factors," Jim said. "We're never going to cure a disease that isn't a disease but [rather one] that's a syndrome or a phenotype. We need to do better than that."

And, just as preeclampsia is not one disease, he believes there is not one way to treat it. "The use of aspirin, for example, is extraordinarily safe but only minimally effective and requires highly elaborate testing to determine who can get it," he said. "There may well be a form of preeclampsia that aspirin is just wonderful for, but that is not yet known."

Moreover, "what is needed is an approach to identify the characteristics of women for whom aspirin is beneficial, in whom ascorbic acid is beneficial, in whom some other anti-inflammatory strategy is beneficial," he said. "That is where researchers are going to make a difference in addressing preeclampsia." Jim believes that the key to resolving the complexity of preeclampsia and other adverse pregnancy outcomes is collaboration, sharing ideas, data, and biologic materials.[37]

When asked about the future for maternal-fetal healthcare, Jim said, "The people I'm training now are amazing. There are some really bright people asking very important questions. I think that we're in really good shape for the future."

Speaking to those aspiring to a career in academic medicine, Jim said: "It's the best life you could lead. Where else do you meet people just like [you] who are weird enough to be up at 4 AM, who are willing to write grants that won't get funded many times, who just keep pushing on?" Jim emphasized that the real privilege of being a physician scientist is caring for patients and the reward of helping people combined with the intellectual challenge of science, "You can't do better."

Life Beyond Research and Clinical Care

Jim's best friend and the love of his life is his wife, Jane Mason Butler, a former midwife who became a world champion rower in her 60s. Jim has three children: Elizabeth, a successful architect, recently profiled in *The New York Times* (https://www.nytimes.com/2019/05/01/style/brooklyn-townhouse-architect.html?smid=nytcore-ios-share) who lives in New York with her husband, internist Michael McKnight; Matthew, a high school teacher and volleyball coach in Seattle, Washington, where he lives with his wife Rachel Butler, a consultant and life coach; and Amy, an exercise physiologist, who passed away in 2005 at the age of 40. An endowed scholarship fund, the Amy Roberts Health Promotion Award for Young Investigators, was established in her memory by the Magee-Womens Research Institute and Foundation. Awarded annually, the scholarship assists young investigators who are interested in influencing patient health and well-being through techniques of behavioral modifications. Jim also has three young grandsons whom he brings together for family vacations twice yearly, once for Thanksgiving hosted at his home, and again for a tropical vacation.

Since joining the Global Pregnancy Collaboration, Jim has been able to see a lot of the world and often extends his business travel into a vacation with his family. Jim and Jane are lifelong fitness enthusiasts who enjoy swimming, rowing, and cycling. Jim also reads as a form of escape, even if the book isn't the best literature or a great intellectual endeavor. He can't recall having ever gone to bed without reading, even during his days on call at the hospital. He prefers fiction and, in particular, mystery novels; two of his favorite authors are John D. McDonald and Craig Johnson.

A film aficionado, Jim enjoys movies and cannot pin down a specific favorite but said his "weirdest" favorite movies have been introduced by his 10-year-old grandson. Having read the popular *Diary of a Wimpy Kid* series, the youngster brought along the movies during a visit with his grandparents. On viewing them, Jim said: "They were so wonderful, the joy of being a young child who is not like everybody else. There were so many lessons in it."

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SUPPLEMENTAL FIGURE 1

James receives a plaque from Dr Roberto Romero for being recognized as a "Giant in Obstetrics and Gynecology" by the *American Journal of Obstetrics and Gynecology* (Perinatology Research Branch, Detroit, MI)

Romero. A profile of James Roberts. Am J Obstet Gynecol 2019.

SUPPLEMENTAL FIGURE 2

Jim with his family on vacation in Mexico. From left: son-in-law Michael McKnight, daughter Elizabeth, daughter-in-law Rachel Butler, son Matthew, and wife Jane

Romero. A profile of James Roberts. Am J Obstet Gynecol 2019.

SUPPLEMENTAL FIGURE 3

Jim and his wife Jane with their grandson Dean

Romero. A profile of James Roberts. Am J Obstet Gynecol 2019.

SUPPLEMENTAL FIGURE 4

Jim and his wife Jane on a bike ride in Tuscany

Romero. A profile of James Roberts. Am J Obstet Gynecol 2019.