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Cover Story

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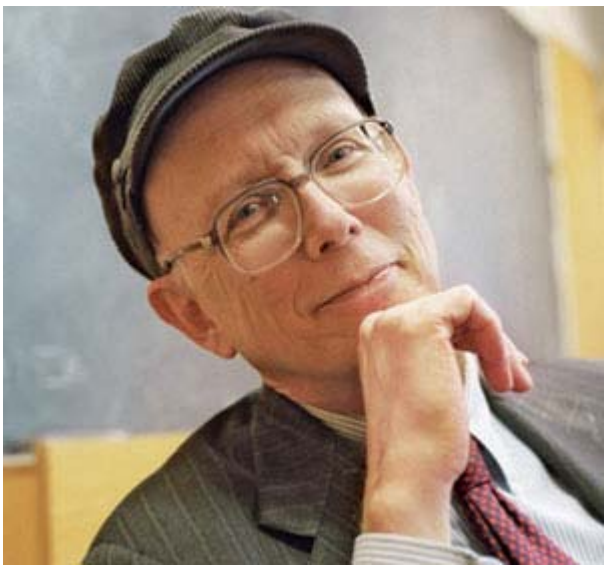
Always On The Move

George M. Whitesides, this year's Priestley Medalist, has influenced academia, government, and industry

Celia Henry Arnaud

GEORGE M. WHITESIDES is so busy that it can take months to book him for an appointment. The Harvard University chemist i in demand as a speaker and as a member of advisory panels. He's on the boards of directors of several companies he helped start. The 67-year-old chemistry professor maintains a travel schedule that would exhaust people half his age. He manages to d all this while directing an ambitious and productive research group of more than 40 students and postdocs. He also teaches at Harvard. It's his perennially dense portfolio of contributions to chemistry that has earned him this year's Priestley Medal, the American Chemical Society's highest honor.



Harvard University Photo

Priestley Medalist Whitesides, Woodford L. & Ann A. Flowers University Professor at Harvard, is this year's Priestley Medalist.

When he's actually in town in Cambridge, Mass., Whitesides' day typically begins with a 7 AM meeting with whomever happene to make it onto his schedule that day, followed by coffee at the Science Center cafeteria. His wife, Barbara, often joins him for morning coffee because it's the easiest place to catch up with him. After that, his day passes in a blur of classes, meetings, and other work that can last until 9 at night. Fourteen-hour days are routine.

That level of activity lends Whitesides an intense demeanor that is at odds with his more relaxed nature. His friends get to see a side of him that others often miss. Where strangers and acquaintances see an intimidating figure, his friends and family see a warm, modest man with a good sense of humor. Whitesides finds humor in most things. "Life is miserable if you take it seriously he says.

No matter how busy he is, Whitesides makes time for his family, including his wife of 37 years and their two grown sons, George T. (not junior) and Benjamin. George T. remembers his father taking the time to come to his hockey games. Whitesides, not you typical hockey dad, sat in the stands, cheering when his son was on the ice and correcting papers or editing manuscripts when h wasn't. When Whitesides travels, which is often, he calls home daily.

Photographer Felice Frankel, senior research fellow with Harvard's Initiative in Innovative Computing, is a collaborator and friend She occasionally gets frustrated when Whitesides' schedule delays projects, but she says: "He's been an incredible friend. Whe

he decides to be your friend, it's for life."

"Of course, he's driven and intense, but you don't feel it," says Jeremy R. Knowles, a longtime friend and colleague who is currently the dean of the Faculty of Arts & Sciences at Harvard. "With many people of such intellect, you feel it. With George, yo recognize it, but you know you're in the presence of a warm human being."

Still, the breadth and depth of Whitesides' knowledge and interests can make people feel inadequate. Carmichael Roberts, a former postdoc who has continued to work closely with Whitesides in business settings, has seen people simultaneously nervou and excited about meeting Whitesides. "You just have to be comfortable that it's okay not to know what he knows," Roberts says

"I don't want to paint George as some warm, fuzzy teddy bear," Roberts stresses. "He's very direct, very transparent, no dancing around an issue," Roberts says, adding that Whitesides doesn't hesitate to question positions that make no sense to him.

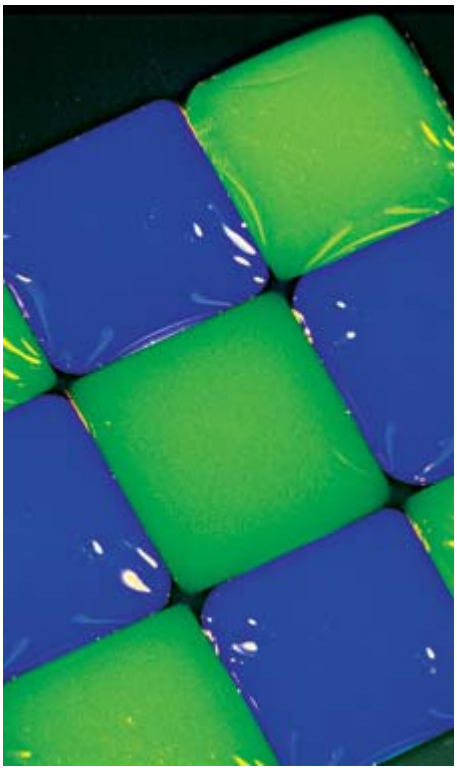
Whitesides suspects that his directness may be the source of his reputation for aggressiveness. "I've never seen any reason if I don't understand something not to ask why. As soon as you start asking why, you very rapidly reach the edge of the universe. When that goes on at a seminar, people get embarrassed."

In addition, Whitesides senses an insensitivity in the way he asks questions. "I'm pretty dispassionate," he says. "I'm not trying to embarrass people, but I would like to know the answer, and I don't like a half answer or waving of hands. Unfortunately, it's easie to ask questions than it is to answer them."

Whitesides describes himself as "curious by nature." Given that curious nature, people might be surprised by what originally attracted him to chemistry—washing glassware. As a teen, Whitesides worked as a technician at his father's chemical engineeri firm in Louisville, where one of his tasks was cleaning glassware. He says he found it "soothing."

WHEN CHALLENGED about the draw of such mundane tasks, Whitesides explains: "Any profession consists of a lot of routine stuff and occasionally really interesting things. If you like the routine stuff, the whole thing is okay."

Although he enjoyed those summer jobs, he entered Harvard as a freshman trying to decide between chemistry and mathematic Although he says he was "perfectly adequate" as a mathematician, the department at Harvard believed that a merely adequate student had no real future in mathematics. His professors there encouraged him to focus his energy elsewhere.



Courtesy of Felice Frankel

Checkerboard A thin hydrophobic self-assembled monolayer separates the hydrophilic squares, which each contain a dyed wate droplet. The image, versions of which garnered the cover of Science and appeared in the book "On the Surface of Things," marked the beginning of the collaboration between Whitesides and Frankel.

With his mathematical machinations thwarted, Whitesides turned to chemistry. There was only one problem: He was failing his

analytical chemistry course. "What can I do?" Whitesides recalls asking the professor. The reply? "Well, I guess you'll have to learn the material," the professor said. Whitesides proceeded to do exactly that.

In preparation for his imminent exams that pivotal semester, Whitesides in a matter of weeks worked through the entire term's worth of material until he understood the answers. He aced the exam, and in recognition of the work that went into that achievement, his professor gave him an A for the course, too. Whitesides became a chemistry major, graduating from Harvard with a bachelor's degree in 1960. What was to evolve into a top-tier career in chemistry was born.

Whitesides has made contributions in a number of fields ranging from nuclear magnetic resonance spectroscopy to organometa chemistry to surface science. He has served on government advisory boards and founded companies to commercialize discoveries. He has brought science to lay audiences through his collaboration with Frankel to which he contributes a love and understanding of molecular phenomena and she brings a genius for expressing these realities pictorially. In 1997, the two published a stunning merging of word and picture in a book titled "On the Surface of Things."

His graduate career benefited from the same kind of fortuitous midcourse correction that turned him into a chemist as an undergraduate. While still at Harvard, he won a National Science Foundation predoctoral fellowship that could be used for graduate study at any university. He applied to the University of California, Berkeley, but the school never responded to his application or subsequent inquiries. He contacted Caltech and asked if he could do graduate studies there instead.

Caltech's chemistry department welcomed him, but few research groups there had openings. By luck, he ended up in the John D Roberts laboratory. His graduate research focused on applying NMR spectroscopy and density matrix calculations to the study o Grignard reagents.

As a grad student in the early 1960s, Whitesides was a solitary researcher who often toiled late into the night with folk music on the radio to keep him company. He had practical reasons for his schedule, including the late-night availability of large blocks of time on the NMR spectrometer. "Every once in a while, something interesting would happen in terms of science," Whitesides recalls, noting that what mostly sustained him was a feeling that the entire process was "just great fun."

He found the applied mathematics to be the most interesting part. Says Whitesides: "I did density matrix calculations in a period when organic chemists not only did not do density matrix calculations but had never heard of a density matrix." (Density matrices are a form of quantum mechanics that can be applied to the spin systems that NMR analyses detect.) Roberts admits that he learned about density matrices from Whitesides.

In the acknowledgments of his dissertation, Whitesides thanked Roberts for his "indirection"—the freedom to go his own way. "There was an enormous amount of autonomy in the group. People could basically do what they wanted to do," Whitesides says He has used such an approach himself, even with his own children. Neither son has followed in his father's footsteps, nor did Whitesides ever push them toward careers in science. "My father's fundamental philosophy toward childrearing was that kids ne to figure it out for themselves," says George T. He now is the executive director of the National Space Society in Washington, D.C. Ben is the lead singer of an indie rock band, the Joggers, and lives in Portland, Ore. Some of this love for music could well have had paternal roots: George Whitesides enjoys classical music and plays the classical guitar.

Roberts treated his students as colleagues, and Whitesides later brought that approach to his own research group. "There are certainly roles for a research director in setting strategies and coming up with good ideas, but a research group does not run wel the only source of ideas" is the research director, Whitesides says. "Had I been raised in a different research group in which the expectation was that all ideas come from the research director, I would have started from a different point. Where I would have ended up, I don't know."

Courtesy of Barbara Whitesides

Family Man Whitesides and his wife, Barbara, with their sons, George T. and Ben.

In September 1963, Whitesides went straight from Caltech to an assistant professor position at Massachusetts Institute of Technology. (His Ph.D. was officially conferred in 1964, thanks to a once-a-year system of granting degrees.) Whitesides doubts

he would have benefited from a postdoctoral position. "I was eager to go off and do my own thing," he says. "If you have reasonably good taste about what's new, then you might as well go do it."

During his early days at MIT, Whitesides played the role of "the group postdoc." He had a bench in the lab with the students, and he didn't get an office for four or five years. Whitesides helped develop the experimental techniques that the group used in their studies of air-sensitive organometallic compounds.

Whitesides cultivated a collegial environment from his first days as a professor. Group members from all eras of his teaching career recall such a team spirit. "Nobody ever said that you worked 'for' George Whitesides; you worked 'with' him," says Charle P. Casey, a former Whitesides student. "He was always trying to get people to take ownership of their problems, to come up with their own ideas of what to do next, and to encourage that kind of independence." Casey, now an emeritus professor at the University of Wisconsin, Madison, and former ACS president, was Whitesides' first graduate student.

As a grad student in the 1970s, Ralph G. Nuzzo came to MIT knowing that he wanted to work with Whitesides. He camped outside Whitesides' door to persuade him to take him on. Like Casey, Nuzzo felt that he collaborated with Whitesides rather than worked for him. Their collaborations continued even after Nuzzo took a job at Bell Laboratories. Nuzzo, of Italian descent, affectionately refers to Whitesides as his "goombah," which colloquially means godfather. Nuzzo is now a chemistry professor at the University of Illinois, Urbana-Champaign.

"When you're working with George, you really are part of the team," says former postdoc Milan Mrksich, now a chemistry professor at the University of Chicago. "He does a great job of bringing out the best in each of his coworkers. He's clearly the smartest person in the group and the person with the best intuition and the broadest knowledge of many areas of science and engineering."

From his earliest days as a professor, Whitesides has had a goal of inventing techniques that can be widely disseminated. His group has had the greatest impact in areas where they developed techniques that were adopted by the broader community, especially soft lithography and microcontact printing, which are techniques for fabricating intricate microscale patterns and features in a variety of materials.

IN THE CASE of surface chemistry, one thing just naturally led to another. The group started by studying polyethylene surfaces. Then Whitesides became involved with the characterization and application of the alkanethiol-terminated self-assembled monolayers invented by Nuzzo and David L. Allara, currently a professor of polymer science and chemistry at Pennsylvania State University. That work flowed into soft lithography work, in which the self-assembled monolayers are used as templates for the formation of patterns on a surface. "George started thinking of self-assembled monolayers as a strategy for dealing with the difficult and cost-centric problems associated with [traditional] lithography," Nuzzo says.

The work in soft lithography further developed into microcontact printing, in which soft lithography is used to create stamps that can be used to transfer patterns on a surface, much as stamps can be used to transfer ink to paper. "The idea of trying to do a one-to-one replacement of lithography with microcontact printing was an audacious aspiration," Nuzzo says. "There will be applications whereby huge areas of commercial practice are going to be impacted by all sorts of unconventional approaches to fabrication and integration."

In little more than a decade, soft lithography and microcontact printing have become standard techniques in many areas of engineering and materials science. "It's so standard that many young graduate students in engineering labs don't always know that those methods were developed by the Whitesides laboratory," Mrksich says.

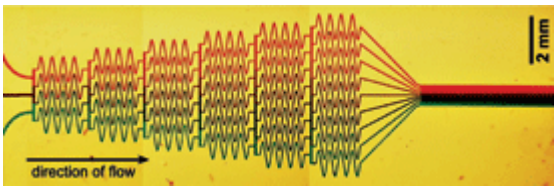
Whitesides no longer studies those self-assembled monolayers and soft lithography techniques for their own sake. Instead, he uses them to address questions in other areas, such as cell biology.

Whitesides edged toward biological research and got his first taste of multidisciplinary teamwork at MIT. Shortly after joining the faculty, he was invited to join an NSF-funded biotechnology project in the chemical engineering department because the organizers couldn't convince a biochemist to participate. Whitesides was young enough and curious enough to accept the invitation. That project gave Whitesides an opportunity to work with biologists and to learn the basics of a field that he still works today. Much of Whitesides' later work using enzymes for organic synthesis, developing biocompatible surfaces, and fabricating microfludic devices for cell biology stems from that initial collaborative project.

In 1982, after 19 years at MIT, Whitesides moved across town to accept a position at Harvard. Nostalgia for his undergraduate years at Harvard played no role in his decision to move, he says. In fact, he is hard-pressed to come up with an explanation beyond needing a "change of scenery." He acknowledges that his style of research, with its emphasis on practical problems, remains better attuned to the engineering spirit at MIT.

At Harvard, Whitesides' group has continued its evolution from one that focused on physical organic chemistry to one that uses chemistry as an entrÃ©e into many other disciplines. When John A. Rogers, now a materials science and engineering professor

at the University of Illinois, Urbana-Champaign, was a member of the Society of Fellows at Harvard, he worked with Whitesides. "Chemistry was the core expertise that provided the competitive advantage, but there was no sense of chemistry as a narrowly defined discipline. It was chemistry to solve problems, not necessarily to do chemistry," Rogers says. That's why it made perfect sense in Whitesides' context to take a core of chemistry knowledge and expertise into areas like electronics or optics or biology, Rogers continues.



Anal. Chem.
Good Gradients Three incoming streams of fluid are divided and recombined, creating a gradient across the channel perpendicular to the direction of flow. Whitesides' group uses such fabrication methods to pattern gradients on microfluidic surfaces to study chemotaxis of neutrophils and to control the orientation of neurons.

The problems in Whitesides' group are selected for their impact on society, Rogers observes. "Everything is scientifically interesting at some level," he says. "In the space of all scientifically interesting things, why not select those things that have the potential for long-term impact?"

Whitesides also lets his interests guide him in picking research problems, focusing on questions that he thinks are important yet also tractable and instructive. "We don't make a clear distinction between science and technology," he says. "We try to make a distinction between good and bad or well done and poorly done." He subscribes to Thomas Kuhn's distinction between puzzles and problems, and he believes they both have their place. "In the accumulation of evidence that comes with puzzle solving is often buried those things that become very important indicators that there's a problem somewhere that has to be solved," Whitesides says.

Whitesides has switched research areas many times in his career. "Some people could look at George's work and wonder how h has entered fields, tackled tough problems in them successfully, and then moved on. He has done that repeatedly by asking fundamental questions of what seemed to everyone to be virtually intractable problems," Knowles says. "He has the fundamenta creative fearlessness of a real experimental scientist." Whitesides is "one of the most eclectic scientists I know," Knowles says.

Mark S. Wrighton, now the chancellor of Washington University, St. Louis, has known Whitesides since they were both professo at MIT. "Sometimes when people become so great in the breadth of what they're doing, you wonder if they have the intellectual ability to be really deep," he says. "George is willing to dive into areas where he doesn't know a lot and to invest the time needed to learn and understand the critical issues that need to be addressed."

Convincing the community to accept those career shifts is tough. "If you have spent the first 20 years of your career working on x and you try to move to y, the community will usually kill you," Whitesides says. His average tenure in an area has been about 10 years. "When we moved out of organometallics, I remember there were all kinds of people who were really annoyed because we were doing good work with organometallic mechanisms, there were lots of good problems in organometallic mechanisms, and w didn't know anything about this other stuff." Whitesides' research direction has changed so often since the beginning of his caree that he has had people—usually younger ones—ask him if he's related to the George Whitesides who once studied organometallic chemistry.

ONE OF THE SIGNS that it's time for him to move on is when many other people are successfully pursuing an area. "If we're no doing something unique, why do it?" Whitesides asks. "It's a big expensive group with very smart people. Unless we're doing something that is different from what other people can do, I don't see any reason we should be doing it."

Teri W. Odom, a former postdoc at Harvard and now an assistant professor at Northwestern University, remembers Whitesides telling her that "if you're working in an area that everybody is working on, you're going to have to be much smarter or much more creative and much better" to get ahead of the game.

Rarely, however, does an area become uninteresting to Whitesides. It's just that "other things become more interesting," he says Now his tastes tend to run to big-picture problems. He has programs studying the origins of life, applications of cutting-edge science to developing-world problems, and complexity, which he defines broadly as systems with interacting components.

For many Whitesides group members, their time in his group introduces them to problems they have never considered. Whitesides pushes boundaries for many of his group members.

"You ask yourself what you've gotten yourself into, because 80% of what he says you don't understand," Mrksich says. "There's real intimidation in realizing that the kinds of projects you might be working on are in areas you've never thought about before ar that George seems to know a great deal about every topic."

"George always challenges you to think about bigger problems," Odom says. "I was trying to describe some small things that I might be interested in, but he kept forcing me to put them into a broader context."

Odom thinks that Whitesides' lab is a "playground" for postdocs, who can choose from a number of different areas. "George is a generalist only in the sense that he has interests in a lot of areas of science. For postdocs, that's great because you've had specific training in something and now you explore more general questions," she says. "For students, unless they are disciplined to dig deep into a problem, they might just acquire a lot of general skills or general expertise."


Courtesy of Barbara Whitesides
All Grown The Whitesides family gathers at the wedding of George T. and Loretta Hidalgo.

Whitesides himself suggests that his current interests are a better fit for postdocs than students. Since coming to Harvard, his group has traditionally been split evenly between grad students and postdocs, but the balance has shifted toward postdocs in recent years. "I find that the kinds of problems that are good for graduate students are not necessarily the kinds of problems I'm interested in right now," he says. "The questions that are most interesting to me are questions of origins of life or complexity or things like that where it's hard enough to define the question, let alone solve it."

MANY PEOPLE enthuse about Whitesides as a mentor. "George will give people a chance that other people won't necessarily b willing to offer," says Mara Prentiss, a collaborator in the physics department. "A lot of people to whom George has given a chance have really thrived." Many alumni have adopted scaled-down elements of Whitesides' approach in their own groups.

Teaching is an important and rewarding part of Whitesides' job. He views himself as the major beneficiary of his teaching experiences, because it forces him to think about new ideas or about old ideas in new ways. "If you can explain something to yourself, you might be able to explain it to freshmen," he says. "I have spent many hours between 11 at night and four in the morning thinking about the very simplest parts of science because there was a lecture the next day."

Whitesides and Prentiss team-teach a nanotechnology course to Harvard students who aren't majoring in science. "One of George's great gifts is to transform extremely difficult ideas into a form that is both comprehensible to a lay person and correct," Prentiss says. "He puts a huge amount of effort into telling them exactly the way it works without having to use concepts they do understand."

Whitesides and Prentiss divide the lectures between them, making it possible to accommodate Whitesides' hectic travel schedul They also try to make a personal connection with the students by offering to have lunch or dinner with every student in the class

This spring, Whitesides is a member of a team offering a course in introductory physical sciences for chemistry and physics students. His portion of the class will deal with issues of entropy and information. "Information can be thought of as the negative entropy," he says. "I intend to ask myself questions about the information content of the cell." Teaching the class will give him ar opportunity to think about issues he hasn't made time to think about before. "It seems to me I'm the big winner," he says.

Through his collaboration with Frankel, Whitesides has had an opportunity to bring science to a general audience as well. Their book "On the Surface of Things," which featured photographs by Frankel and accompanying descriptions of the science of surfa phenomena by Whitesides, will be published in an updated version this fall.

Another way that Whitesides is bringing his work to a larger audience is by commercializing it. He has been involved in approximately a dozen start-ups over the years. His passion for companies grows out of his problem-solving approach to scienc "I think universities have an obligation to try to make what they do real," he says. At the same time, he recognizes that a university's first responsibility is to its students. He believes that students shouldn't be assigned a "boring research problem" to obtain beneficial results for a company. The easiest way to avoid such a situation is to "have students work on the next compan he explains. That is, have students work on science "that with luck in 10 years might be something interesting."

Universities and industry, Whitesides believes, play complementary roles in the goal of making a better society. "To say that the should be no contact between the two is crazy, and to say that the two should be fused is crazy," he says. "It should be a good marriage."

Whitesides is careful to keep the research in his group distinct from that in companies he's involved with. For example, the company NanoTerra, based in Cambridge, is working on commercializing soft lithography as a manufacturing technique. Whitesides still uses soft lithography within his academic group, but they pursue different applications. In another example, Theravance, based in South San Francisco, is a biotech company that is developing polyvalent drugs. Whitesides still studies polyvalency, which refers to molecular entities with multiple binding sites, but his current interest is in why antibodies are divalen Both of these companies use intellectual property developed in Whitesides' lab.

Whitesides has been intimately involved with each of the companies he helped cofound. The most successful to date has been GelTex Pharmaceutical, which was bought by Genzyme for about $1.3 billion. GelTex was not based on Whitesides' intellectual property. Harry Mandeville, a former Whitesides grad student who was also the first employee at GelTex, jokes that he wants to remain Whitesides' number one student—the one who made the most money for Whitesides. Whitesides does not use the mone he earns from companies to fund research in his lab, although he does use prize money that way.

IN ADDITION to his academic and industrial work, Whitesides has a strong sense of public service. He has served on many advisory panels in the Department of Defense and at the National Academy of Sciences, of which he has been a member since 1978. Last year, he served on the committee that wrote the report "Rising above the Gathering Storm," a congressionally requested report that recommends ways to improve American competitiveness in science and technology. He is the current chairman of the Committee on Science, Engineering & Public Policy (COSEPUP) at the National Academies. The committee conducts studies on issues in science and technology policy that cross disciplines and monitors developments in U.S. science a technology policy for the academies' leadership.

Ralph J. Cicerone, president of the National Academy of Sciences, has observed Whitesides at committee meetings. "He likes t be guided by the facts," Cicerone says. "He's willing to follow the evidence wherever it leads."

Cicerone had to convince Whitesides to accept the COSEPUP position. Whitesides "raised good counterpoints and fair questior about whether his time would be well used and how he thought it would be best used," Cicerone says. "Life is now sufficiently fu that if I do x, I have to throw y overboard," Whitesides says.

As he approaches his 70th birthday, Whitesides shows no signs of slowing down. "Retirement intrinsically suggests that you would prefer to do something else," says George T. "I don't think my father currently feels that he would prefer to do anything els He's got such a frankly rich and varied professional career right now and, relatively speaking, so much flexibility, that I don't think he really sees a reason to stop."

When asked about plans for retiring, Whitesides doesn't really answer. He claims that he and his wife, Barbara, are in a contest, the winner being the first to die. He says, only partly joking: "My hope is that at some point I'm run over by a streetcar." In the meantime, he plans to continue working. "I've never seen George more interested than he is now," Barbara says.

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