A reprint from
American Scientist
the magazine of Sigma Xi, The Scientific Research Society

The Forgotten Father of Epigenetics

A theory put forward in the 1930s by E. E. Just, embryologist and African American, shares surprising connections with our emerging understanding of development.

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Despite the strides that have been made in recent decades to increase minorities' involvement in science, African Americans are still significantly underrepresented in scientific disciplines. A 2010 survey, for instance, showed that blacks make up only 5 percent of the science and engineering workforce, even though they make up 13 percent of the US population. Yet diversity is important not only for fairness in representation; it is also critical for enhancing creativity in scientific discovery.

In his 1989 book *Discovering*, physiologist and author Robert Root-Bernstein identifies four "inputs" into the discovery process: cultural context, the established body of science, "science in the making," and the scientist himself or herself. The individual scientist, he notes, "will represent a unique mix of hereditary proclivities and environmental experiences."

The importance of cultural context in discovery is demonstrated by the contributions of Ernest Everett Just, an internationally recognized embryologist of the early 20th century who was African American. A graduate of Dartmouth College (1907) and the University of Chicago (PhD, 1916), Just was a professor at Howard University in Washington, DC. He performed research in the first part of his career at the Marine Biological Laboratory in Woods Hole and later in Europe. He authored more than 70 scientific papers as well as two books, both published in 1939. One book was his magnum opus, *The Biology of the Cell Surface*. Known for his study of the structural changes that occur at the egg cell surface during fertilization, Just also was the first to discover that the adhesiveness of the cells of the early embryo are exquisitely dependent on cell surface properties.

In the 1930s Just put forth a bold hypothesis involving nuclear–cytoplasmic interaction to explain how the cells of the early-stage embryo participate in the developmental process. His hypothesis, which he called the "theory of genetic restriction," clashed with the gene theory that was then becoming dominant. I believe that Just's theory—his model of the developing cell—represents a microcosm of his vision of the perfect society, which, in turn, was strongly influenced by sociological concepts circulating within the African American intellectual community at the time.

Although Just's theory of genetic restriction was hotly debated among his contemporaries, it did not significantly influence the development of biology, for several likely reasons. First, the dominance of the nucleocentric view of the cell that accompanied the gene theory served to shift attention away from more cytoplasm-centered views. Second, unlike other scientists, Just did not have a cadre of students to continue his work, because as an African American he was unable to obtain a position at a research-intensive university, which would have enabled him to have a year-round research program. Instead, he worked essentially alone in the summer at Woods Hole or during trips to Europe. Third, the experimental methods that would have been required to test the theory did not exist at the time. Fourth, due in part to his outspokenness in challenging prominent biologists and his gravitation toward European biology, Just was treated as an outsider by his American counterparts. Because of this, and simply because he was African American, he was viewed as a controversial figure. This made his peers less likely to embrace (and cite) his work. As historian Kenneth Manning notes in his biography *Black Apollo of Science*, even though younger scientists who heard Just present his theory at the 1935 meeting of the American Society of Zoologists wrote for reprints and saw him as "one of the most creative men in zoology in the United States," they, along with everyone else, declined to take up the challenge to advance his work. As a result, his theory has lain dormant.

Just's theory has many redeeming qualities, and he was uniquely positioned to advance these ideas because he was able to see things differently than his peers. He held convictions that were not only rooted in his experimental work, but were also informed by his particular life experiences. These convictions gave him an intensity of purpose that his peers did not have.

Just's Social and Cultural Milieu

Just's intensity of purpose was shaped by the oppressive social environment in which he lived. The first half of the 20th century was marked by Jim Crow laws that enforced racial segregation across the southern United States, including Charleston, SC, where Just

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grew up, and Washington, DC, where he lived as an adult. Influential scientific eugenicists—including Henry F. Osborne, president of the American Museum of Natural History, and Charles Davenport, Harvard zoologist and director of the Cold Spring Harbor Laboratory—were arguing at the time that blacks were biologically inferior to whites. They believed that the races of humankind had evolved separately from an ancient hominin species in geographically distinct areas and were separate subspecies that could be arranged hierarchically, with whites at the top and blacks at the bottom.

The African American community, faced with this onslaught of racist propaganda and crushing social discrimination, did not sit idly by. Intense intellectual activity within the black community served to powerfully counter the accusations of racial inferiority. W. E. B. Du Bois, president of the National Association for the Advancement of Colored People (NAACP) and a prominent sociologist at Atlanta University, in both his writings and speeches, waged war against the assertions of inferiority. In an essay titled "The Negro Scientist," published in 1939, he challenged an argument being made at the time that blacks were not suited for the rigors of science. In words that still resonate, he stated that the small numbers of African Americans in science were not due to any inherent limitations of blacks but were because of racial discrimination. He argued that scientific creativity knew no boundaries, and that by denying African Americans access, the nation was cutting itself off from the benefits of a diverse scientific workforce.

A Harvard graduate and close associate of cultural anthropologist Franz Boas of Columbia University, Du Bois believed that race was not biologically based, but was derived from the shared history and culture of a people. He encouraged a sense of pride among African Americans. He wrote about the "talented tenth" that included the foremost American black intellectuals of the time. E. E. Just, arguably the most famous African American scientist in the world at the time, would have been a member of this elite group. So, too, would Alain Locke, a professor and close colleague of Just's at Howard University who was known as the "philosopher of the Harlem Renaissance."

Ernest E. Just, shown here in his laboratory at Howard University in 1916, was a prominent embryologist of the early 20th century. Perhaps because of his race, some of his ideas, including one that predicted epigenetics, did not get their due. (Photo courtesy of Scurlock Studio Records, Archives Center, National Museum of American History, Smithsonian Institution.)

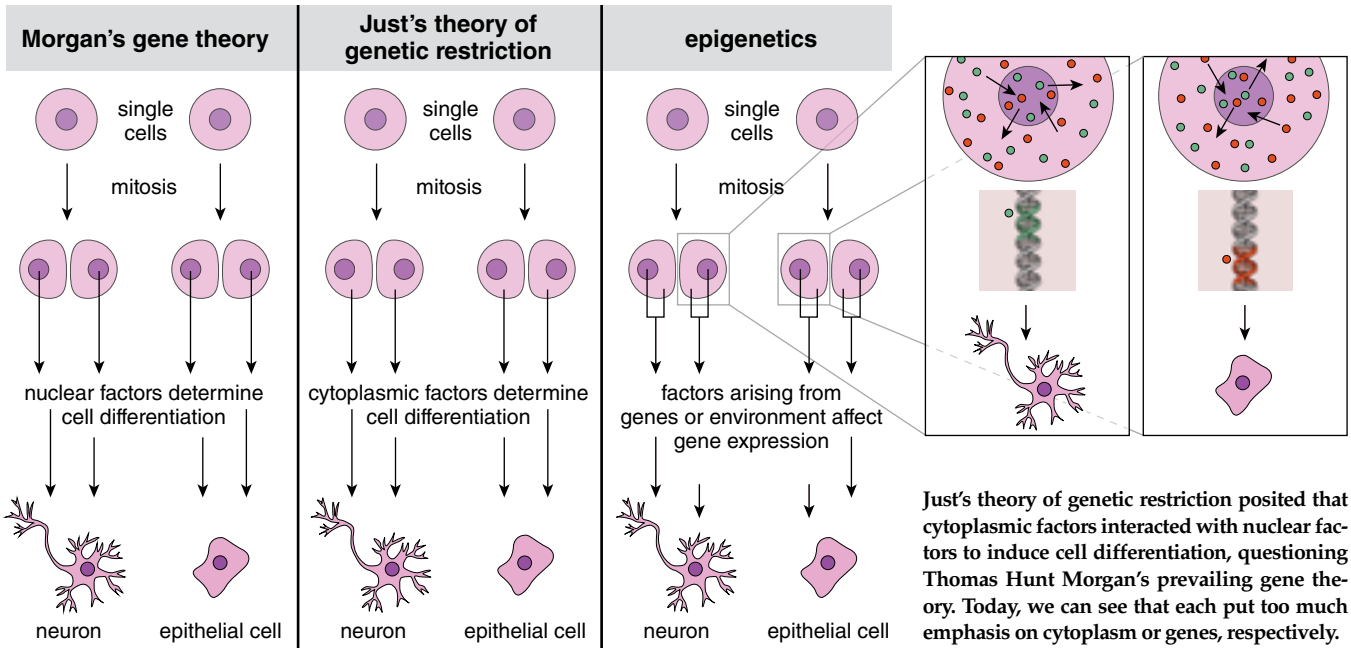
A philosopher turned anthropologist, Locke argued that nations will succeed when they foster cultural exchange among different ethnic groups. He emphasized that the healthiest societal relationship is one in which each group is able to offer something of value to the other, and each group respects the autonomy of the other. Just, a friend of Locke's, was certainly familiar with his ideas. Kenneth Manning relates how Just was especially impressed with Locke's knowledge of African American culture and history, and with his enthusiasm for the way that blacks were beginning to break free of "the psychology of imitation and implied inferiority."

It was Just who invited Melville J. Herskovits, a student of Boas who authored the groundbreaking 1941 book *The Myth of the Negro Past*, to spend a year (1924 to 1925) as a visiting professor at Howard. A proponent of the notion that race is a sociological and not a biological concept, Herskovits showed that blacks possess a vibrant culture that is tied to their ancestral African homeland and is not derived from or inferior to mainstream American culture. Just and Herskovits kept up an active correspondence long after Herskovits left Howard.

Considering Just's intellectual milieu, it strikes me as highly likely that he was affected by the ideas about race and cultural dialogue articulated by scholars such as Du Bois, Locke, Herskovits, and Boas. These social ideas likely exerted a powerful influence on Just as a creative scientific agent.

Just's Novel Theory

As these events were broadly unfolding in American society, dramatic change was also taking place in biologists' view of the genotype-phenotype relationship in embryonic development. Thomas Hunt Morgan, an embryologist at Columbia University who won a Nobel Prize in 1933, was leading an effort to establish the new field of genetics. Based on his experiments on the fruit fly, Morgan proposed that physical units of inheritance called *genes* are arranged in linear fashion on chromosomes in the cell nucleus. In his influential book *The Theory of the Gene*, Morgan called for the separation of the new field of genetics from that of classical embryology. Whereas embryologists, including Just, believed that all components of the cell were important in inheritance and development, Morgan and the new geneticists believed that the nucleus played the dominant role and that genes controlled all events of the cell throughout the developmental process.



Just's theory of genetic restriction posited that cytoplasmic factors interacted with nuclear factors to induce cell differentiation, questioning Thomas Hunt Morgan's prevailing gene theory. Today, we can see that each put too much emphasis on cytoplasm or genes, respectively.

As the disagreement between genetics and embryology began to widen—creating a gap that has only recently begun to close with the advent of evolutionary developmental biology—several people tried to bring about reconciliation. One of these was Just. In *The Biology of the Cell Surface*, he presented an explanation for how cells participate in development. It was one that was in direct opposition to Morgan's gene theory. Calling it the theory of "genetic restriction," his explanation focused on nuclear–cytoplasmic interaction, and it gave the more important role to cytoplasmic rather than nuclear agents.

Just's stated goal was to explain the mystery of differentiation—how different types of cells arise in the developing embryo. He described the difficulty that Morgan's gene theory encountered in trying to explain differentiation: "For how could the genes be responsible for differentiation, if they are the same in every cell? Unless the geneticists assume that their genes are omnipotent, we cannot understand how the problem of differentiation can be solved by the gene-theory of heredity." He explained how, according to his own experimental data, nuclear material increased during the embryonic cleavage process. He observed that "no individual nucleus in any blastomere [a cell of the early embryo] at the end of cleavage ever vanishes. On the other hand the total quantity of nuclear substance … is greater at the end than at the beginning of the cleavage-period."

Reviewing the evidence, Just reasoned that what is true about the cleavage process is true about the whole developmental process: Nuclear mass increases overall. But out of what is nuclear material synthesized? Observing that the total amount of cytoplasm decreases during the same time period, he proposed that "nuclei are built up from the cytoplasm. So too their constituents, the chromosomes."

Just then presented his theory: "The progressive differentiation of the egg during cleavage … is brought about neither by the pouring out of stuffs by the chromosomes into the cytoplasm nor by segregation of embryonic materials [a rival theory at the time proposed that differentiation occurred via the selective redistribution of preexisting egg factors into different regions of the embryo]… but by a genetic restriction of potencies through the removal of stuff from the cytoplasm to the nuclei." Thus, the job of the nucleus in each type of cell is to selectively sequester a subset of materials from the cytoplasm, "leaving others free. The free materials determine the character of the cell—as ectoderm, mesoderm, or endoderm."

In Just's view, the nucleus is more like a passive holding pen than the seat of power that the geneticists had imagined. The important players are the cytoplasmic agents, which, with help from genes, are free to go about their vital tasks of giving the various cell types their particular properties. Genes play a secondary role of absorbing this or that factor. We know now that Just was incorrect in denying a central role for genes. His theory was too cytoplasm-centered. But Morgan was not correct, either; his theory was too nucleocentric.

Nearly 80 years later, we can see imperfections in Just's theory. Cellular differentiation occurs in part because of differential gene expression, whereby proteins known as *transcription factors* enter the nucleus and bind to particular regions upstream of genes, thereby stimulating or repressing their transcription. It is the differential expression of genes in cells of various tissue types that can explain the cells' diverse characteristics. We have learned that there is an almost electronic circuit–like pattern of expression of different sets of genes in various types of cells and during different stages of development.

Because of the Encyclopedia of DNA Elements (ENCODE) project, we now know that gene expression is much more complex than previously thought. The genome's activity is dependent on a whole array of factors and processes. Transcription factors are important, but so are other features. The patterns of chemical modification (methylation, acetylation) and the particular three-dimensional structure that the chromatin—a complex of DNA, RNA, and proteins that makes up chromosomes—has can affect gene expression. Moreover, epigenetic regulation can occur through the post-transcriptional modification of messenger RNAs, which encode proteins, or through their degradation or inhibition via the binding of micro-RNAs.

Noncoding RNAs—that is, RNA transcripts that do not code for proteins—also play direct roles in regulating gene expression. Moreover, ENCODE revealed that 80 percent of the DNA in the human nuclear genome is "functional" in the sense that either transcription factors (or other proteins) bind to it, or it is being actively transcribed into RNA. Many of these transcripts are noncoding, and their roles are largely unknown at this point.

We are realizing that there is an extensive highway of interaction among factors originating in the cytoplasm and the genes located in the nucleus. Moreover, physical processes are increasingly being recognized as important. The old model in which there was a one-way flow of information from DNA to messenger RNA to protein—the process envisioned by the early 20th-century geneticists, which developed into what is known as the central dogma—is becoming increasingly untenable. Indeed, with the recent rise of epigenetics, which deals with the ways that extranuclear factors interact with genes to bring about the organism's phenotype, it is looking more like Just was on to something. Although he was wrong about some of the details, he was absolutely right about the importance of nuclear–cytoplasmic interaction.

Unique Cultural Influences

In his writings, Just espouses a conception of how the cell works that was in conflict with that of the emerging field of genetics. This made me wonder: Where did Just's bold ideas come from? Why did he believe so strongly that all of the parts of the cell are important in the developmental process?

Based on what I knew about the cultural milieu in which Just was immersed, I wondered whether his notion of the "federalism of the cell" (to use a phrase coined by biologist Scott Gilbert of Swarthmore College) was influenced by concepts of race and race relations that were circulating within the African American community at the time. Recall that the role of the nucleus during differentiation, according to Just's theory, was to sequester factors from the cytoplasm, allowing the ones that remained to steer the cell in a particular direction. Genetic restriction removed certain potencies from the cytoplasm, "leaving others free."

Notably, African Americans at the time were striving to break free of an oppressive, segregated society. Though marginalized, the black community had many talents. I believe that Just's ideas about the important role of the cytoplasm during cellular differentiation were influenced by these *sociological* concepts that were prominent at the time. I believe that, in Just's view, the cell represented a microcosm of a human society in which groups that had been seen as marginal in fact play the more important role.

The notion of using nonscientific ideas in the formulation of scientific hypotheses has deep precedent. Biologist Francisco Ayala discusses in his recent book *Darwin's Gift to Science and Religion* the ways hypotheses can arise. He writes that "[s]cientists, like other people, come upon new ideas and acquire knowledge in all sorts of ways: from conversation with other people, from reading books and newspapers, from inductive generalizations, and even from dreams and mistaken observations."

Borrowing from other realms as one formulates hypotheses is not uncommon. For instance, according to Root-Bernstein, the 19th-century German cellular pathologist Rudolf Virchow drew parallels between biological development and the development of a society. Likewise, Harvard paleontologist and author Stephen Jay Gould was deeply influenced by his belief in dialectical materialism. And it is well known that Charles Darwin used the ideas of Thomas Malthus, the British economist who believed that a population's survival depended on its growth rate and the availability of resources, in formulating his theory of natural selection.

Darwin had traveled around South America on the *HMS Beagle* as a young man and also spent a childhood exploring nature. He had seen a great diversity of life. One could argue that Darwin, more than anyone else (except perhaps Alfred Russel Wallace, co-discoverer of natural selection), was singularly prepared to make these particular contributions to biology.

In a similar way, Just was best prepared to make the particular contributions that he made to our understanding of nuclear–cytoplasmic interaction during development. It seems reasonable to me that he could have forged a hypothesis about how the cell works using ideas percolating within his intellectual circle. After all, Just was more exposed to the ideas than his peers. Further, these ideas would have had more immediacy for him than for others, because he was black. In the same way that the seed that crystallized Darwin's theory came from the apparently unrelated field of economics, so it was African American social thought that informed Just's theory of how the cell works in development.

Why Diversity Is Essential

Diversity is critical for the scientific enterprise. We do not know where the next Darwin or Just will come from. This future person will have a unique set of experiences and background. Who can say what life experiences will spawn an idea that revolutionizes our understanding of nature? To stifle diversity—or not actively encourage it—is to diminish the creative engine of science.

Though forward-looking in its epigenetic orientation, Just's theory did not have a significant impact on biology for a number of reasons, including the fact that his peers sidelined him because they did not know what to make of him. Simply by excelling, he was challenging all of their notions about what African Americans should be like. He was, as Swedish economist Gunnar Myrdal said, "the quintessential example of an American dilemma."

But the story of Just's theory is important today because it highlights why diversity is critical for science. We need representation from all of society's various groups in part because equal representation helps ensure a more unbiased assessment of merit. But the need is even more fundamental: A diversity of ideas, which can originate from ethnic, cultural, and other forms of diversity, is the very life blood of science. Without it the stale ideas of the past might continue to circulate unabated, to the detriment of the scientific enterprise.

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