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PAKISTAN IN CRISIS
by Steve Coll

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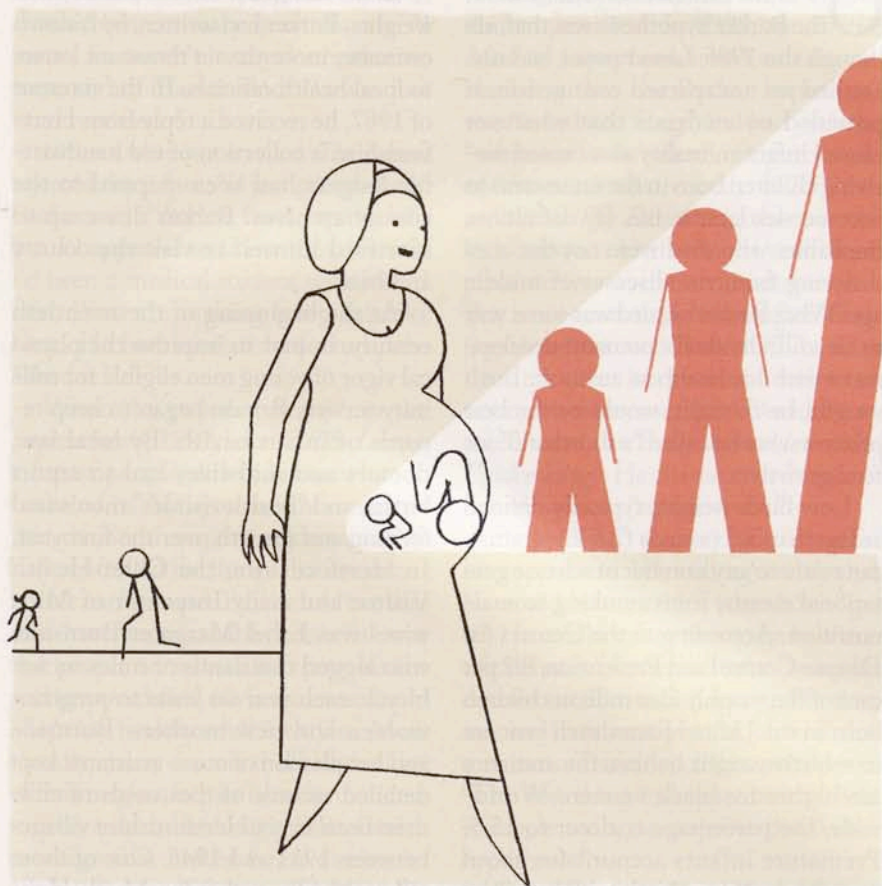
issue about why death rates in *newborn* babies were so low in London.”

Barker is given to wearing the same rumpled clothes for days on end, and, as he once put it, has “never been anything other than the shortest boy in school.” He is effortlessly sarcastic. Now sixty-nine, he has a head of white hair over dark eyebrows, a ruddy face, and a low voice that

start from very well-nourished communities, with tall churches and tall people,” Barker said. But because agricultural wages were extremely low, wage riots broke out in the nineteen-twenties, and many young people migrated to London. “They brought with them all the advantages of having had a well-nourished childhood, and the women

pothesis”—was first published, in *The Lancet*, it was regarded as heretical. Barker took this as a personal rebuke. In his telling, the critics expected him to “just go away.” Instead, he cast a wider net for more historical data. He was keen to get his hands on one particular statistic: birth weight.

Now, when Barker lectures, he shows slides of the red-and-green heart-disease map and an arresting 1912 photograph of barefoot street urchins from London’s East End. “You live in two worlds,” he said at a recent talk at Princeton, “the world of your mother and the world into which you are born.” He made disparaging asides about the “dismal failure” of genetic research to explain chronic diseases. And, as he does often these days, he ended with a pledge to “fix” the problem. For Barker, this includes injunctions about the diets of young girls and the risks of low birth weight and, more surprising, the unsettling suggestion that underweight toddlers might be better off not growing too fast—that there might be advantages in the small remaining, relatively speaking, small.



Low birth weight seemed to raise the likelihood of illnesses like heart disease.

often descends to a whisper. His office bookshelves are crammed with scientific texts and with his mother’s editions of Thackeray and Austen. Barker is a good storyteller, and he relished getting to “the mystery of London” because it advertised an approach to epidemiology—not just number-crunching but also social history, economics, and narrative stitchwork—that his admirers find highly imaginative and his critics find maddening.

“London renewed itself through the nineteenth century by bringing in the fittest young people—men and women, but particularly women who went into domestic service. They came from the villages,” he said, people born and raised in England’s prime agricultural country, to the east and south of London. “You

gave birth to healthy babies, who tended not to die,” he said.

Those women posed the question that would shape the next twenty-five years of Barker’s scientific career: Was vulnerability to heart disease rooted in adulthood, in childhood—or did it go all the way back to life in the womb? “And London said it’s for sure about life in the womb, or newborn babies at most,” Barker told me. That led him to the next question: Was the trajectory toward disease perhaps set by how healthy the mother had been even before her childbearing years?

In 1986, when Barker’s basic claim that heart disease was “related to nutrition during prenatal and early postnatal life”—now known as the “Barker hy-

Like many people of his generation, David Barker had a childhood that was shaped by the Second World War. He was born in London in 1938. His father, a mechanical engineer, joined the military when the war began; his mother, a violinist, took him to live in a small village called Much Hadham, in Hertfordshire, north of London, as part of the evacuation of children from London during the blitz. His younger sister was born there in 1943.

After attending the British public school Oundle, Barker went on to medical school at Guy’s Hospital, in London, and trained as an internist before beginning graduate studies in epidemiology at the University of Birmingham. In 1972, he accepted an offer to join a new medical school that was being built in Southampton, a gritty port city heavily bombed by the Germans during the Second World War. It was far from Oxford and Cambridge, the twin jewels of British academic science, and Barker simultaneously cultivated and resented his outsider status. (“We’ve done very well being big fish in a small pond,” he told me one day.)

In 1980, on the day after Easter, Barker’s wife, Angela, died after a long

battle with mental illness, and Barker found himself, at age forty-two, the single parent of five children, ranging in age from six to eighteen. His epidemiological work all but stopped. Then, in 1983, Barker married Jan Tarplett, who was divorced and had three children of her own. In addition to taking care of eight children, Jan embroidered art works to illustrate the covers of his books; she sewed wedding dresses for several women in his lab group; and, in 1986, she found Manor Farm, a fourteen-acre homestead in East Dean, between Southampton and Salisbury. "My own Barker hypothesis," Osmond told me, "is that without Jan, David would have been sunk."

Barker, who believes that much of modern biology has become estranged from the natural world, takes frequent walks along the River Dun, a chalk stream that runs through Manor Farm. Sometimes the river has the quality of a moat. There is a sense of isolation there, one that may stem, at least in part, from the strong antipathy Barker's work initially provoked. The intensity of the reactions made me wonder if people were responding to the theory or to the scientist. Barker has an ability to infuriate, and a tendency to make sweeping statements. (At one point, as he was explaining again that the issue is not just what women eat during pregnancy but, rather, their lifetime dietary habits, Barker told me, "A woman is merely the arena for miracles over

which she has no control.") A scientist who has worked on the fetal-origins hypothesis told me that Barker "is very aggressive in talking about it, and I think he has made himself enemies that have been unhelpful. That's been his style. I'm not sure it's been necessary or optimal."

One of the earliest reservations about the Barker hypothesis was that, although the 1986 *Lancet* paper had unearthed an unexpected connection, it provided no evidence that whatever caused infant mortality also caused surviving children born in the same areas to become sick later in life. By definition, the babies who died were not the ones suffering from the diseases of middle age. What Barker needed was some way to tie an individual's prenatal development with his health as an adult. Birth weight, he thought, would be the best proxy—what he called "a shorthand" for fetal growth.

Low birth weight, typically defined as less than 5.5 pounds (2.5 kilograms), can relate to any number of adverse gestational events, from smoking to malnutrition. According to the Centers for Disease Control and Prevention, 8.2 per cent of the roughly four million children born in the United States each year are low-birth-weight babies; the statistics are higher for black women. Worldwide, the percentage is closer to 15.5. Premature infants account for about two-thirds of low-birth-weight babies

in the United States, while the vast majority of such cases in the developing world—more than ninety per cent—are due to nutritional deprivation and poor maternal health during gestation. (Barker's initial research did not involve premature babies, since only the hardest from the first half of the twentieth century survived.)

In his search for old records of birth weights, Barker had written, by his own estimate, more than a thousand letters to local health officials. In the summer of 1987, he received a reply from Hertfordshire: a collection of old handwritten ledgers had been shipped to the county archives. Barker drove up to Hertford himself to visit the county archivist.

At the beginning of the twentieth century, in part to improve the physical vigor of young men eligible for military service, Britain began to keep records of infant health. By local law, doctors and midwives had to report births, and "health visitors" monitored feeding and growth over the first year. In Hertfordshire, the Chief Health Visitor and Lady Inspector of Midwives was Ethel Margaret Burnside, who logged thousands of miles on her bicycle each year on visits to pregnant women and new mothers. Burnside and her platoon of nurse assistants kept detailed records of thousands of children born in six Hertfordshire villages between 1911 and 1945. One of those villages happened to be Much Hadham, and one of those children was Barker's sister.

"The guy was sitting there with these books on his desk, saying, 'I can see your point, but you can't have these records. We've put them under a fifty-year hold because of the comments that were written by the midwives and health visitors about some of the mothers,'" Barker said. "And it was the fact that on his desk were the records from Much Hadham, where I had lived, that unlocked them for us. I would not have gotten those records unless I had been able to align myself up as a local person." Hertfordshire officials eventually agreed to transfer the birth records to the University of Southampton.

It took two years for Barker and his colleagues to find the adults whose birth records they now possessed. They ini-



"And your wife called to remind you not to have sex with anyone on your way home."

tially tracked down 5,654 men who were born between 1911 and 1930 (men were easier to trace than women because their last names didn't change when they got married), and then correlated mortality and health data with birth weight and infant growth. Men who had weighed 5.5 pounds or less at birth, and especially those who remained small at age one, had the highest rates of death from coronary heart disease. "I mean, we weren't in any doubt that we were right," Barker said. "It was just very, very clear."

Others were not so sure; *The Lancet* rejected the paper. "It just got trashed," Barker said. "And so I rang up the editor. I happened to know him, because I'd been a medical student with him. I said, 'You are making a big mistake here.' He had another look, and published it."

When the paper appeared, in the September 9, 1989, issue of *The Lancet*, a lot of people didn't know what to make of it. Many were unconvinced that the Southampton epidemiologists had controlled for things like socioeconomic background; Barker told me that one "not unreasonable concern" was that people born small into poor homes and impoverished environments would adopt less healthy adult life styles. More broadly, many doctors disliked the idea of fetal origins, in part because it undermined a decades-long public-health message that linked heart disease to adult behavioral factors. The late Sir Richard Doll, Britain's leading epidemiologist, told Barker that he was "very disappointed," and Barker heard that as an understated but unmistakable form of academic censure.

While many heart-disease experts had responded to the Barker hypothesis with hostility—"People were starting to walk out on meetings when I spoke," Barker said—another group, biologists who studied prenatal development, couldn't hear enough. "I didn't know what it meant," said Kent Thornburg, a physiologist at the Oregon Health & Science University, who encountered Barker for the first time at a conference in 1989. "But I knew it was incredibly important."

In rapid succession, new epidemiological studies confirmed and extended the observations of the *Lancet* paper.

When epidemiologists found birth records in India, in South Carolina, in China, and in Sweden, the same basic pattern emerged: slow growth in the womb, as suggested by low birth weight, seemed to increase the risk of adult illnesses like coronary heart disease, hypertension, type 2 diabetes, and stroke.

Even as the body of evidence grew, doubts persisted. In 1995, the *British Medical Journal* published an editorial implying that the Barker hypothesis was "broad and fuzzy" and had yet to be "subjected to an ordeal" of rigorous scientific attack. As recently as 2002, an article in *The Lancet* argued that the link between birth weight and blood pressure was overstated and minimal. But more recent epidemiological findings have favored Barker. "The idea that this effect is a statistical artifact or not real is nonsense," said David Leon, an editor at the *International Journal of Epidemiology*. He characterized some of the critiques as "mischievous."

Barker hasn't always made it easy for his supporters. His colleagues say that he would berate critics who didn't "get it." He would refuse to engage in scientific debates. He seemed to be daring his detractors to prove him wrong. But that, too, had its advantages. As Johan Eriksson, one of Barker's collaborators, put it, "The best thing to happen to this field is people trying to disprove the Barker hypothesis."

One of the most significant events in the life history of a scientific idea occurs when its detractors become adherents. A Danish researcher, Allan Vaag, told me that he "really did not believe in this theory" until 1997; that was the year he discovered, in a study of identical twins, that diagnoses of type 2 diabetes were more common for the twin who had a lower birth weight. Janet Rich-Edwards, a Harvard Medical School epidemiologist with the Nurses' Health Study, which has tracked about a hundred thousand women since 1976, admitted that she "set out to prove that Barker was totally wrong." But, in 1997, Rich-Edwards and her colleagues reported "strong evidence" of a connection between low birth weight and a heightened risk of coronary heart disease and stroke. In 2000, Rich-Edwards and her Harvard colleague Matthew

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(See page 58)

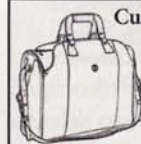
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Gillman published a paper titled "The Fetal Origins of Adult Disease: From Sceptic to Convert."

On a windswept, rainy day in February, 1995, Johan Eriksson, a young Finnish doctor, arrived at Manor Farm for a visit. In his restless search for early birth records, Barker had begun to suspect that there was a gap in the story. All along, there had been hints from the epidemiology that how much and how fast a low-birth-weight child grew might also matter a great deal. That first evening, after dinner, Barker remembers telling Eriksson, "The thing we really, really need, beyond everything else, is some records of growth in children whose size at birth had been measured."

Eriksson replied, "I have them."

In the early nineties, intrigued by the Barker hypothesis, Eriksson and his colleague Tom Forsén had launched a search for Finnish birth records. "I was certain we would find them somewhere," Forsén told me. "I just didn't know how many." They found exquisitely detailed birth records of fifty-three thousand babies born at Helsinki University Central Hospital between 1924 and 1944, which included not only birth weight but size of the placenta and measures of the mother's body composition. They also found thousands of school growth cards and child-welfare-clinic cards. The Finnish researchers then set out to track down the adults these children became.

In 1971, Finland began to issue a personal identity number to every citizen; this number was used to register hospital admissions, prescriptions, socioeconomic data, and, eventually, cause of death. By painstakingly collating these records, the researchers managed to assemble comprehensive pictures of the infancy, growth, and health of thousands of Finns.

In 1997, the first paper based on the "Helsinki cohort," as it came to be known, appeared in the *British Medical Journal*. The study showed that thinness at birth seemed to be linked to the child's vulnerability to later disease and that small size at age one was associated with adult mortality from heart disease. The mother's body composition also played a role. Women who were small

because their own growth had been affected by poor childhood nutrition often produced low-birth-weight babies. Short women who were overweight, Barker said, were the "most dangerous scenario" for heart disease in their offspring, while tall women could become overweight without dramatically affecting the disease prospects of their children. Fifty-four papers have been published to date on the Helsinki cohort, with another twenty-three in preparation, and they have been consistent in their findings. Osmond said, "Our best estimate is that every one kilogram increase [in birth weight] reduces heart disease by about seventeen per cent. The effect with diabetes seems a bit stronger."

The Helsinki data, as summarized in a 2005 paper in *The New England Journal of Medicine*, suggested that the biggest threat to adult health, however, was rapid gain in body mass index (a standard, though imperfect, measure of body fat) in a child who had a low weight at birth and had been small and thin during the first two years of life.

"What the Finland paper shows is that the children who are going to bankrupt the American health system are not fat children," Barker said. "They are thin children who are putting on weight at age two, three, four, five, six, and so on. That's a difficult thing to say. These are invisible children."

On a sunny spring afternoon at the University of Southampton, a biologist named Tom Fleming offered Barker and me a cup of tea, and then gave us a harrowing tour of some recent experiments with animals. Fleming was among the earliest to test the Barker hypothesis experimentally by asking what could biologically explain the correlation between birth weight and later disease.

In one study, Fleming's group fed pregnant rats a low-protein diet for the

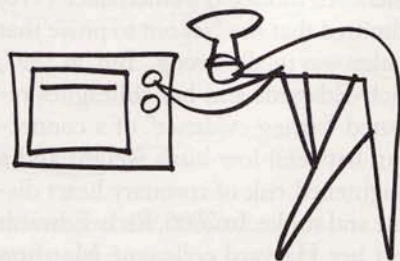
first four days after fertilization. The researchers then gave the rats normal diets for the remainder of gestation. Yet that four-day period exerted profound and irreversible long-term effects. The embryos had fewer stem cells than those of pregnant rats fed a normal diet and, after birth, had differences in organ size, weight, growth, and metabolic function, including blood pressure.

"The way I understand things now," Fleming said, as Barker listened intently, "is that the embryo is having a kind of dialogue with its mother about nutrient availability. And that dialogue will result in appropriate compensatory mechanisms if, for example, nutrition is poor."

Even at this very early point—at an analogous stage, most women would not even know they were pregnant—Fleming believes that the embryo can detect reduced levels of insulin and essential amino acids, as well as elevated levels of glucose, in the blood of its mother. If those nutrient levels are limited or unbalanced, the embryo must adjust—either by extracting more nutrition from the mother or by slowing down its own growth. "The most critical thing for the embryo is that it engages in a growth trajectory that is appropriate for its nutrient availability," Fleming said.

Back in 1992, Barker and C. Nicholas Hales, a biochemist at Cambridge, attributed the development of type 2 diabetes disease in adults to what they called the "thrifty phenotype." The idea was that the fetus set its metabolic thermostat during critical periods of gestation. If the setting was "thrifty," because of less than optimal fetal nutrition, the individual would be metabolically and physiologically ill suited to adapt to the nutritional prosperity of postnatal life in most developed countries. A person whose metabolism had been programmed to deal with its mother's poor diet, for example, would be overwhelmed by a plentiful childhood diet, and put on fat rather than acquire muscle mass.

Barker calls the kidneys, which regulate blood pressure, "a pretty piece of biology." During a brief developmental window, between the thirtieth and thirty-sixth week of gestation, the fetus calibrates the number of blood-cleansing kidney units, or nephrons, it needs to



make. Full-term low-birth-weight babies possess as much as thirty to forty per cent fewer nephrons than higher-birth-weight babies. In the nineteen-nineties, Barry M. Brenner, a nephrologist at Harvard Medical School, proposed that these babies would be at greater risk for high blood pressure as adults—a prediction that subsequent research has borne out. If a small and thin baby puts on weight quickly after infancy, the likelihood of kidney dysfunction in adulthood increases, too. “If you’re small and you grow rapidly, you’re overwhelming your reserve capacity,” Brenner said. “You’re stressing the system.”

There is keen medical debate, and conflicting scientific data, about the optimal growth of a child between birth and age two. When I asked Barker about it, he made sure to say that no child is doomed by low birth weight; rather, knowledge of the risks should allow doctors to identify heightened vulnerability in certain children, for whom preventive measures can make a great deal of difference. But, he said, “The two messages for parents are: the nutrition and growth of your baby in the first two years after it’s born is important, and, broadly, the more it grows, the better. Growth is good. But *after* two, the rules change, and it’s better if babies stay in their tracks”—for a small child to stay small—“rather than starting to go up through the centiles.”

Since 2003, Barker has held a position at the Oregon Health & Science University, in Portland, and he and his wife have established a foundation dedicated to optimizing the growth of infants and children. In February, O.H.S.U. began to enroll young women in a pilot project to monitor their diet, health, and, eventually, pregnancies. “We are going to alter the nutritionally poor environment of people in Oregon,” Barker said in a recent talk. “We don’t know how to do it, but we’re going to try.”

Pronouncements like that carry vexing implications. “In many of the closed-door meetings, with five or six or ten scientists sitting around the table, this becomes a very hot debate,” Thornburg said. Matthew Gillman, of Harvard, believes it is not only nutrition but the entire maternal milieu—diet, stress, hormones—that affects intrauterine growth, and said that there is no reason to change current recommendations to pregnant mothers,

which are to avoid smoking, increase the consumption of fish, and eat a balanced diet. Of course, those recommendations can be confusing enough—eat fish, but not too much of fish that might be high in mercury. Barker’s work expands that bubble of anxiety.

The Barker hypothesis has, gradually, acquired its own air of orthodoxy. When I used the word “controversial” to describe it in a recent conversation with Richard Schultz, who studies early development at the University of Pennsylvania, he quickly took exception. “A few years ago, it was considered controversial,” Schultz said. “But it’s my sense that it’s no longer controversial, and people have moved on. The discussion now is about what are the underlying cellular and molecular mechanisms.”

Given Barker’s frequent caustic references to “modern-day hereditarians,” perhaps the most ironic turn in the story of the Barker hypothesis is its convergence with a new field of biology known as epigenetics, which refers to the way environmental factors can produce permanent changes in the activity of genes. Researchers have recently found that subtle nutritional changes in the diets of rats and mice can turn off certain genes in the developing fetus, with lifelong effects on metabolism and growth.

Barker is, typically, impatient with principally genetic explanations. “Genes are not Stalinist dictators,” he said. “They live in a democracy, and what they do is conditioned by what else is going on around them. If geneticists find molecular mechanisms for this, bully for them! It’s just not where I live,” he said. “I can’t wait twenty years for the geneticists to figure this out before we start improving the nutrition of human babies. You know? One-quarter of all babies born in Southampton are recognizably thin. This will lead to shorter lives as a group. We need to fix it!”

Later, when we spoke in his office, he said, “How much do we need to know about how it works at the cellular and molecular level to fix it? Maybe we don’t need to know anything very much.” He added, “You almost can’t say that—it’s such a deeply held belief that you have to really understand something before you fix it. But I don’t believe that’s how it will work out.” ♦

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