From rags to research

As a child, geneticist Mario Capecchi had to fight for survival after his mother was imprisoned by the Nazis. He tells his story to Carina Dennis, hoping to inspire others from a disadvantaged background.

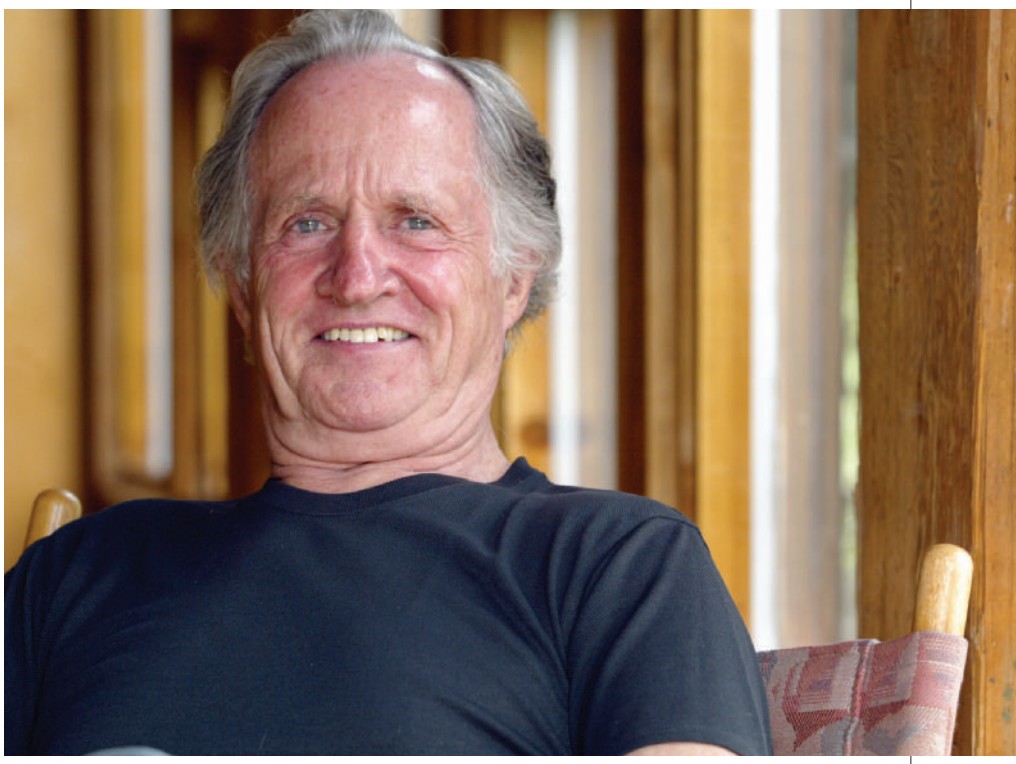
Hunger focuses the mind. And hunger is what Mario Capecchi remembers most from his early childhood, which was spent on the streets of war-torn Italy. Today a contender for a Nobel prize, the geneticist attributes the single-mindedness and fearlessness that has underpinned his scientific success to this formative struggle for survival.

Capecchi, who works at the University of Utah in Salt Lake City, is fêted for his contribution to methods for selectively knocking out genes in mice — widely used to investigate gene function and to create animal models to study human disease. Yet while he was conducting the experiments that made his name, none of Capecchi's peers knew of his harrowing childhood experiences.

When he spoke out for the first time, while accepting a Canadian prize for medical science in 1993, Capecchi shocked even his wife, who had heard only snippets of the tale. "Subsequently, I wrote about the story when I received the Kyoto prize in 1996," he says. "To make sure that there were no more surprises I showed her a draft of the manuscript."

Capecchi's life story is humbling. Born in Verona in 1937, he was the product of a brief relationship between Lucy Ramberg, a poet, and Luciano Capecchi, an Italian air-force pilot. Nearly four years later, his mother — who was one of the Bohemians, a group of artists outspoken in their opposition to the Nazis — was taken away by the Gestapo and interned in the Dachau concentration camp.

Before her arrest, Capecchi's mother sold all her belongings and used the money to arrange for a peasant family to care for him. But for reasons Capecchi has never understood, the cash soon ran out. At just four-and-a-half years of age, he was turned out onto the streets. Although he is happy to talk in general terms about his early life, Capecchi refuses to be drawn into the grim specifics. "The reality was brutal and there is little to be gained from recounting the details," he says.



Mario Capecchi hopes that his life story will help disadvantaged people to fulfil their potential.

S. C. WILSON

Slow start

After moving to the United States when the war ended, Capecchi started at elementary school aged nine without knowing a word of English or how to read, write or do mathematics. His teachers said he would never go to college. By talking about his troubled beginnings, Capecchi hopes to encourage lab heads not to dismiss the potential of people from disadvantaged backgrounds. "My message is that anyone in any circumstances can make it," he says.

Capecchi has proved his teachers wrong. So, too, the dismissive reviewers of a grant proposal he submitted to the US National Institutes of Health in 1980, detailing his strategy for disabling genes in mammalian cells. It was too speculative, they ruled.

Undeterred, Capecchi continued the research, diverting funds from other projects. His efforts were rewarded. Capecchi's was one of two groups — the other led by Oliver Smithies, then at the University of Wisconsin — that a few years later showed that a dysfunctional copy of a mammalian gene will, on rare occasions, line up with and replace the normal version, in a process called 'homologous recombination'[1,2].

> "I think it can be an advantage being naive, because you can come up with ideas that haven't been thought of before."

Knockout mice are created by performing this trick in mouse embryonic stem (ES) cells. The transformed cells are injected into embryos, and breeding from the resulting mice produces animals that carry the disabled target gene in all of their cells.

Martin Evans, then at the University of Cambridge, UK, had by the mid-1980s isolated mouse ES cells[3] and showed that they could be incorporated into a developing embryo to create a 'chimaeric' animal[4]. Capecchi demonstrated that homologous recombination also happens in ES cells[5], and developed efficient methods to select the tiny proportion of cells in a culture to have undergone this transformation[6]. The stage was set for the debut of targeted knockout mice, first described in 1989 and 1990 by groups including those led by Capecchi and Smithies[7–11].

Capecchi ascribes his perseverance with this work, despite the initial scepticism of his peers, to his formative experiences on the streets. His childhood fixation on finding food fostered an ability to concentrate on the problem at hand, regardless of distractions. "It's both a strength and a weakness," says Capecchi. Although he can focus intently on a complex research question, he isn't a multi-tasker. "He thinks all these big thoughts but he can't remember where his glasses are," observes one of his lab staff.

When he was left to fend for himself, Capecchi survived by begging and stealing. He

BETTMANN/CORBIS

Shattered streets: Italian children cluster round as Allied soldiers hand out sweets in 1944.

often travelled with other children, operating in small groups. One would create a diversion while the others stole food and other supplies. "But I couldn't stay in one location for very long, because fairly soon everyone would recognize me and what I was up to," says Capecchi. Occasionally he was picked up and put in a hospital or orphanage — mostly brutal institutions from which he soon escaped.

Seven-year itch

His nomadic beginnings are reflected in his science. Capecchi likes to change fields roughly every seven years. He worked on bacterial viruses before moving into the mammalian genetics for which he is renowned. Today, he is interested in the developmental genetics of the nervous system and behaviour.

These transitions required Capecchi to attend conferences as a relative unknown, swot up on new literature, and face other scientists wary of newcomers encroaching on their turf. "They often don't welcome you with open arms," he says.

Given the real horrors that Capecchi has endured, he has never been scared to seem ignorant. "I think it can actually be an advantage being naive, because you can come up with ideas that haven't been thought of before," says Capecchi. "And the broader your experience is, the less fearful you are to try to do different things."

Capecchi credits his love of pursuing big questions to James Watson, co-discoverer of the DNA double helix, who was his PhD supervisor at Harvard University. "He is the most important person in my scientific career," says Capecchi.

But Capecchi's relationship with his famously outspoken mentor wasn't without friction. He recalls the time they disagreed over the results of an experiment on the rates at which the subunits of ribosomes, the cellular bodies that make proteins, come together and separate. Capecchi was not convinced by the data and suspected that an unknown protein might be involved. He wanted to repeat the work; Watson thought the case was closed. When the argument escalated, Capecchi threw glass plates bearing key data into the bin, ensuring that he would not have to publish the results.

Colleagues ducked for cover as Watson exploded in fury and showered Capecchi with expletives. "I came that close to being thrown out of the lab," Capecchi says. But he was right — a few years later a ribosomal dissociation factor was discovered[12].

Meeting the quietly spoken Capecchi today, it is difficult to imagine him being confrontational. He shuns large conferences, and prefers to keep his research group to a manageable size of about ten postdocs and five graduate students. "I don't do well in large groups," he admits.

Joint effort

Within this cohesive unit, he encourages a spirit of social interaction and mutual assistance inspired by his adolescent years in a Quaker community. After the war, Capecchi's mother tracked him down on his ninth birthday — she found him in hospital, naked and half-starved. He didn't recognize her. "She had aged a lifetime," he says.

Three days later, the pair boarded a ship bound for the United States to live with Capecchi's uncle, who with his wife had founded a Quaker community north of Philadelphia. Capecchi's mother never recovered from her wartime experiences. "She lived in her imagination for the rest of her life," he says. So it was left to his uncle and aunt to bring up the young boy.

Capecchi's experiences have left him fiercely self-sufficient, and keenly aware of the importance of supportive and inspiring mentors. "He is very open to new ideas and will almost never say no if something broadens the scope of the question," says Matthew Hockin, a postdoc in Capecchi's lab.

When choosing new members of his team, Capecchi applies his philosophy of looking beyond people who have the obvious scientific backgrounds. He puts much more emphasis on applicants' drive and passion, rather than their curriculum vitae. "What I'm mainly looking for is curiosity and excitement," he says.

"Your legacy is who you have trained. I think of them as an extended family who I hope will continue an interesting line of questioning that I helped foster," Capecchi adds. Given his own experiences, he is much more interested in where his protégés end up, rather than where they started. ■

Carina Dennis is *Nature*'s Australasian correspondent.

1. Smithies, O., Gregg, R. G., Boggs, S. S., Koralewski, M. A. & Kucherlapati, R. S. *Nature* **317,** 230–234 (1985).
2. Thomas, K. R., Folger, K. R. & Capecchi, M. R. *Cell* **44,** 419–428 (1986).
3. Evans, M. J. & Kaufman, M. H. *Nature* **292,** 154–156 (1981).
4. Bradley, A., Evans, M. J., Kaufman, M. H. & Robertson, E. J. *Nature* **309,** 255–256 (1984).
5. Thomas, K. R. & Capecchi, M. R. *Cell* **51,** 503–512 (1987).
6. Mansour, S. L., Thomas, K. R. & Capecchi, M. R. *Nature* **336,** 348–352 (1988).
7. Schwartzberg, P. L., Goff, S. P. & Robertson, E. J. *Science* **246,** 799–803 (1989).
8. Zijlstra, M., Li, E., Sajjadi, F., Subramani, S. & Jaenisch, R. *Nature* **342,** 435–438 (1989).
9. Koller, B. H. & Smithies, O. *Proc. Natl Acad. Sci. USA* **86,** 8932–8935 (1989).
10. Thomas, K. R. & Capecchi, M. R. *Nature* **346,** 847–850 (1990).
11. McMahon, A. P. & Bradley, A. *Cell* **62,** 1073–1085 (1990).
12. Subramanian, A. R. & Davis, B. D. *Nature* **228,** 1273–1275 (1970).