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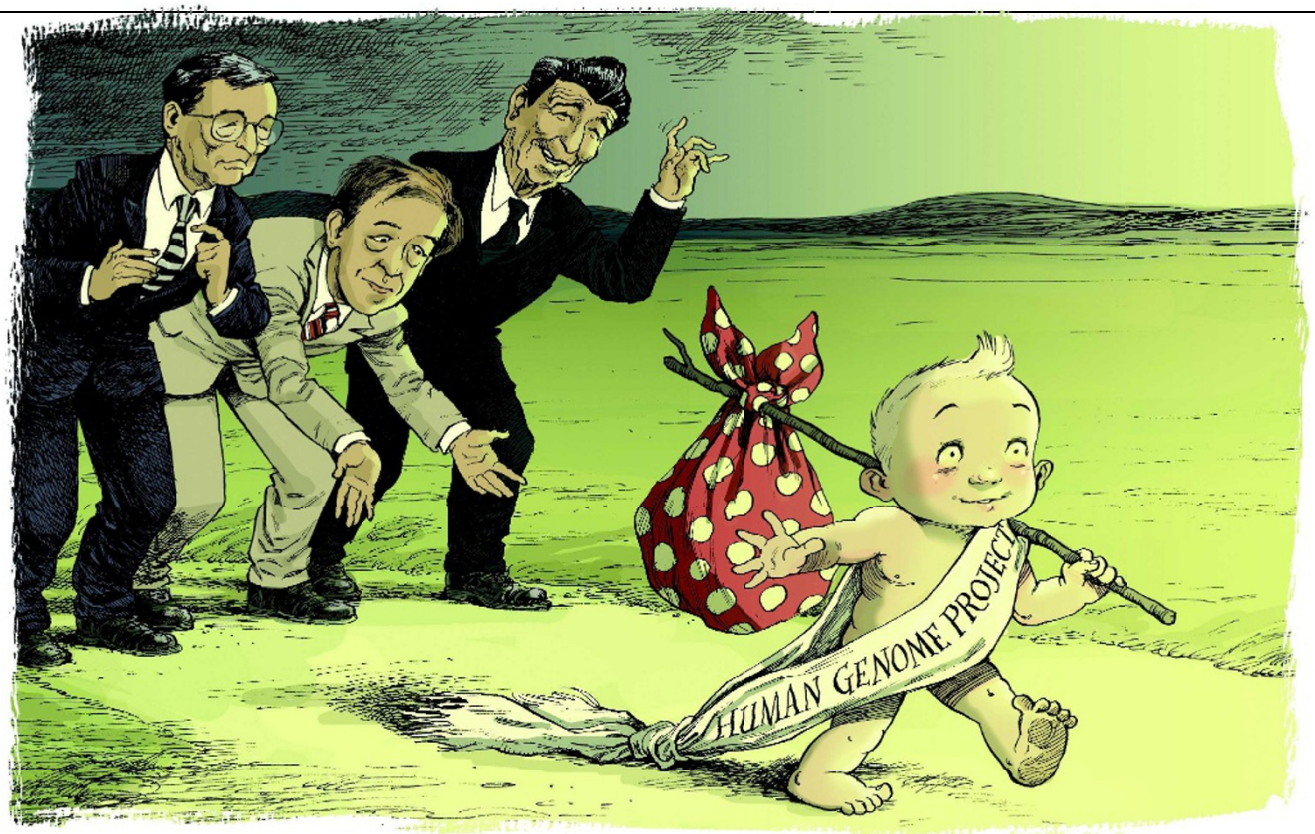

D. PARKINS

Santa Fe 1986: Human genome baby-steps

The 1980s saw plenty of discussion on sequencing the human genome. But, according to **Charles DeLisi**, one conference was crucial for converting an idea to reality.

It was summertime. I had left my job as a senior investigator at the US National Institutes of Health (NIH) to take up a new role as head of health and environmental research programmes at the Department of Energy (DoE). This was not an obvious platform from which to launch an effort to sequence the human genome. In fact, organizing such a project was far from my mind. I did, however, feel strongly that we needed a deeper understanding of the impact of human activities, especially energy strategies, on the global environment.

Central to our mission at the DoE was to understand the effect on human health and the environment from energy by-products, such as fuel emissions. I was especially interested in how modern genetics could be brought to bear on these issues. During my decade at the NIH we would occasionally discuss the nature of resistance and susceptibility to disease among humans. At the DoE, the same thought seemed to be emerging in an entirely different context — how can we genetically characterize variations in the susceptibility of individuals to low levels of energy by-products?

In October 1985, two months after I arrived at the DoE, David Smith, a senior member of the health and environmental research staff, handed me a copy of a report. It was called *Technologies for Detecting Heritable Mutations in Human Beings* and had been written by the now defunct Office of Technology Assessment, whose function was to provide science advice to members of the US Congress.

Not surprisingly, the report had been informed by an earlier meeting on this very topic. That meeting had been organized by DoE staff — David Smith himself and Mortimer Mendelsohn, then head of health and environmental research programmes at the Lawrence Livermore National Laboratory in California. It was clear from this report that real progress towards meeting DoE goals would require bolstering our genetic programmes, and the report hinted at how this might be done.

The idea was to sequence the human genome. It was known at the time that, on average, the genetic difference between two individuals was approximately one base per thousand. So if we were able to sequence one genome, this could act as a reference point for information on genetic differences. I immediately called Mendelsohn, who headed our advisory board at the DoE, and asked him what he thought.

He told me about another meeting organized five months earlier by Robert Sinsheimer at the University of California in Santa Cruz. Sinsheimer, a former biologist at the California Institute of Technology in Pasadena and chancellor of the University of California, wanted to explore the feasibility of sequencing the human genome. I also found out that there had been an earlier conference of scientists in Alta, Utah, to discuss emerging sequencing technologies — although this meeting made no proposal to sequence a full genome.

I then discovered that there was strong interest from leaders in the field, such as Leroy Hood, Walter Gilbert and Charles Cantor, but that the path from idea to implementation was far from clear. Crucially, a human genome project would need substantial funding. Yet the

major funding agencies appeared uninterested, and the idea languished.

Politics and money

Smith and I were eager to sample a broader cross-section of the community, and I asked physician Mark Bitensky, head of life sciences at the Los Alamos National Laboratory in New Mexico, to organize a workshop for leading lights in molecular genetics and allied fields, including the computational sciences. The brief was to assess the costs, value and feasibility of a human genome project, as well as the time needed to complete it. Bitensky was an obvious choice as he had a strong interest in the issues surrounding genetic variation from the point of view of personalized medicine.

The delegates, who gathered in Santa Fe on 3–4 March 1986, included many who had been involved in the earlier Office of Technology Assessment report, as well as several who had attended the Alta summit the previous year. Other prominent geneticists were also present, as were representatives from industry.

Not all were familiar with the history of the idea of sequencing the human genome and, as had been the case at previous meetings, not everyone was comfortable with it. Early on, discussions about costs, organizational architecture and technical obstacles were extremely spirited. There was widespread disagreement over whether it made sense to sequence a genome, more than 80% of which we already knew was non-coding. There was also great concern over the ability to achieve sufficiently low error rates at reasonable cost, and over the US$3-billion price tag. Not to mention the boring and repetitive nature of the project.

There was, however, unanimity about the project's potential value to science (gene regulation, developmental biology, evolution) and to medical applications such as genetic disease and cancer. Interestingly, there is no record of discussion on what is perhaps the greatest beneficiary of the sequencing revolution — infectious disease.

The meeting reached a broad consensus on almost all issues. And although no definitive recommendation was made on how the project would be organized, delegates unanimously recommended forming a steering committee that would help shape a management plan.

The Santa Fe meeting was a success with scientists and also helped to open doors to prospective funding sources in government. Invitations had been sent out to heads of federal agencies asking them to send representatives to the meeting. Only one response came back, and that was an expression of regret. But after the conference, things began to change. The idea of a full genome sequence was now on the national scientific stage, which enabled us to begin the critical task of garnering support from the DoE, the Reagan administration and Congress.

In late April, based on letters I received from participants of the Santa Fe workshop, and on a report prepared by Bitensky, I wrote a memo to Alvin Trivelpiece, the assistant secretary at the DoE to whom I reported. In this I outlined a project that would be divided into three phases: technology development, mapping and sequencing. I also formed a genome advisory committee that included Francis Collins, who went on to head the US Human Genome Project.

Enter the NIH

With Trivelpiece on board, we began to alert Congress and the White House Office of Management and Budget (OMB) to discussions in the scientific community, including the DoE's plans for genome sequencing. The OMB was surprisingly supportive, considering the huge cost and its reputation as a fierce budget-cutting organization. Officials were impressed, both with the unanimity of the Santa Fe workshop on an idea that was unusually ambitious and potentially paradigm altering, and with the fact that this would not be an open-ended science project. It was deliberately pitched in a way that said: this is an engineering/infrastructure-type activity. It has an end-point and well-defined milestones.

I also developed a rapport with the Republican senator from New Mexico, Pete Domenici. Domenici, being from a state that housed two major national laboratories, Sandia and Los Alamos, was accustomed to dealing with abstruse physics projects, and was pleased to have before him a project whose relevance could easily be explained to his constituency. As a member of the Senate's budget committee and a ranking member of the powerful appropriations subcommittee on energy and water development, we needed Domenici to obtain the support of Congress and Administration to move the project forwards.

"Discussions about costs and technical obstacles were extremely spirited."

With support from the Secretary of Energy and the OMB, a $13-million line item initiating the genome project appeared in President Reagan's budget submission to Congress in January 1987. It subsequently passed both Houses, and 1988 saw the first official expenditures on the Human Genome Project.

As the DoE moved forwards during 1986, word of an unprecedented initiative was spreading. At a June 1986 Cold Spring Harbor meeting on the 'Molecular biology of *Homo sapiens*', sequencing the human genome became the topic for an impromptu discussion.

Unlike at Santa Fe, Cold Spring Harbor heard more voices urging caution. Several participants believed that the project would lead to masses of unevaluated data, or that the computational methods available to us at the time would yield relatively little information. This was part of a more general concern that the technology of the day was not appropriate for the complexity of the task.

Other researchers feared that the project would be subject to political interference, as was sometimes seen with NASA, and regarded the DoE as the wrong agency to manage it. For its part, the NIH was concerned legitimately that a large project, spread out over more than a decade, would shift substantial sums of money away from worthwhile investigator-initiated proposals. Nevertheless, James Watson was among those who felt that NIH involvement was crucial. In the summer of 1986, he successfully persuaded Congress to include a human genome allocation as part of the agency's 1988 budget.

I left the DoE in the summer of 1987, feeling naively certain that the project was in safe harbour, and that a complete sequence would be ready by our target date of 2001. We got the date right, but for the wrong reasons. The 2001 date was based on an assumption that the economy would be relatively normal. In fact, the mid-1990s was an incredibly vibrant period economically and stimulated investments from venture capitalists, some of whom made possible the formation of Celera Genomics, the company led by Craig Venter that was at the head of a private-sector sequencing effort. Without the ensuing public versus private competition, it is unlikely that the complete sequence would have been ready by 2001 because the target date was reset to 2006 after I left Washington.

As in all complex human ventures, the Human Genome Project had its share of stresses, squabbles and power plays between different agencies. In the end, everyone that mattered pulled together to create what I regard as a phase transition in national science policy. It is a monumental tribute to the biomedical research enterprise in the United States — not only to the scientific ingenuity that brought it successfully to completion, but to a culture of versatility and adaptability. ■

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