The Alta Summit, December 1984

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Alta is a ski area nestled among the Saguache Mountains in Utah, a winding 40-minute drive southeast from Salt Lake City. From December 9 to 13, 1984, visitors were isolated by repeated blizzards. The slopes were covered most mornings with Utah's renowned fine light powder, which beckoned skiers to cut its virgin surface.

For those 5 days, Alta was also a capital of human genetics. Many historical threads in the fabric that later became the Human Genome Project wind through that meeting, although it was not a meeting on mapping or sequencing the human genome. Through happenstance and historical accident, Alta links human genome projects to research on the effects of the atomic bombs dropped on Hiroshima and Nagasaki 40 years earlier. If genome projects prove important to biology, then historians will note the Alta meeting.

The Alta meeting was sponsored by the Department of Energy (DOE) and the International Commission for Protection Against Environmental Mutagens and Carcinogens. It was initiated by David Smith of DOE and Mortimer Mendelsohn of the Lawrence Livermore National Laboratory, who turned over final organization to Raymond White of the Howard Hughes Medical Institute at the University of Utah.

The purpose was to ask those working on the front lines of DNA analytical methods to address a specific technical question: could new methods permit direct detection of mutations, and more specifically could any increase in the mutation rate among survivors of the Hiroshima and Nagasaki bombings be detected (in them or in their children)? The idea behind the Alta meeting came from another meeting on March 4 and 5, 1984, in Hiroshima, at which new DNA analytical tools were deemed second highest priority for human mutations research, just behind establishing cell lines from atomic bomb survivors, their progeny, and controls. Those attending the Alta meeting in December (see Table 1) were drawn from a variety of backgrounds, and many had never met each other. Most said in interviews later that they came to the meeting quite skeptical, but left thinking it had been one of the best scientific meetings they ever attended (Interviews, 1987, 1988).

The principal conclusion of the meeting was, ironically, that methods were incapable of measuring mutations with sufficient sensitivity, unless an enormously large, complex, and expensive program were undertaken. Technical obstacles thus thwarted attainment of the main goal of the meeting, yet the meeting left a profusion of new ideas in its wake, some of which later washed ashore to be incorporated into various genome projects. Five years later, there is still no sensitive assay for human heritable mutations, but there *are* genome programs at NIH, at DOE, and in several foreign nations.

Excitement about the new methods blossomed at Alta despite, or perhaps because of, the wintry isolation. As Mortimer Mendelsohn noted in his internal report to DOE:

> It was clear from the outset that the ingredients for a successful meeting [were present] . . . and the result far exceeded expectation. Once the point of the exercise was clear to everyone, a remarkable atmosphere of cooperation and mutual creativity pervaded the meeting. Excitement was infectious and ideas flowed rapidly from every direction, with many ideas surviving to the end. (Mendelsohn, 1985)

John Mulvihill began the meeting by reviewing epidemiological studies of human mutations. Studies that could theoretically have detected a threefold increase in mutations had not found any. James Neel spoke about measurement of mutations among Hiroshima–Nagasaki survivors, estimating that the likely mutation rate was 10^{-8} per base pair per generation (or roughly 30 new mutations per genome per generation), indistinguishable from that of Japanese controls and in the same general range as that estimated by epidemiological methods and detection of protein variants among other "normal" populations. Several of the technical consultants commented on the passionate devotion Neel brought to the study of Hiroshima and Nagasaki victims, and how his demeanor set the tone for lively and cooperative exchanges throughout the meeting.

Existing methods had failed to detect an anticipated increase in mutations among the more than 12,000 children of Hiroshima–Nagasaki survivors (whose parents received an average 43 rad). Calculations showed that to measure a 30% increase in the mutation rate, roughly what would be expected from the average dose, one would have to examine 4.5×10^{10} bp in the children, and 4 to 5 times more in the parents (Delahanty, 1986). In fact, the DNA methods were at least an order of magnitude short of being able to detect the expected impact from atomic bomb exposure among survivors; they could only detect differences expected from radiation exposure well above the lethal dose (and hence not measurable). The question was whether there were new technical means that would get around the problems. The answer was no, but the process of thinking about it forced many novel ideas to the surface.

George Church began to ruminate on the ideas that culminated in multiplex sequencing. He said later that discussions with Maynard Olson, Richard Myers, and others helped him crystallize his inchoate ideas. (David Smith recalled watching George Church disappear in a cloud of new-fallen powder one afternoon, and worrying about the future of DNA sequencing technology.)

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TABLE 1

Participants at the Alta Meeting, December 1984

David Botstein	Mortimer Mendelsohn
Elbert Branscomb	John Mulvihill
Charles R. Cantor	Richard Myers
C. Thomas Caskey	James V. Neel
George Church	Maynard Olson
John D. Delahanty	David A. Smith
Charles Edington	Edwin Southern
Raymond Gesteland	Sherman Weissman
Michael Gough	Raymond L. White
Leonard Lerman	

Richard Myers showed work using RNase I to cut (and thus make detectable) single base pair mismatches; he and Leonard Lerman showed early data using gradients of denaturing agents embedded in electrophoresis gels as a way to detect heteroduplexes and mismatches. Myers credits his roommate for the conference, Maynard Olson, with clarifying his ideas and permitting him to expand the RNase I method to mismatches other than C–A mutations. In a trip report to the Office of Technology Assessment, Michael Gough characterized the Church and Myers presentations as technological wonders and called the two young scientists, then largely unknown, the "two biggest surprises" of the meeting (Gough, 1984).

Charles Cantor showed how his and David Schwartz's first pulsed-field gel electrophoresis method could separate megabase-sized DNA fragments, resolving individual yeast chromosomes and thus introducing an enormously powerful method to assess DNA structure on this scale. He also showed his and Cassandra Smith's first macrorestriction digest of the *Escherichia coli* genome, which suggested the tantalizing possibility of physically mapping entire genomes by combining restriction cleavage and pulsed-field gel electrophoresis.

Maynard Olson showed early results of attempting to construct a physical map of *Saccharomyces cerevisiae* using overlapping clones, and also showed good separation of megabase-sized DNA using a modification of the Schwartz–Cantor electrophoresis technique. Mendelsohn's DOE report noted that "while Olson's method would not presently be chosen for analyzing human mutation rates, his philosophy of paying careful attention to and investing in the quantitative, methodological details of DNA technology had a recurrent and important impact on the meeting" (Mendelsohn, 1985). Olson later brought the same core ideas to the National Research Council Committee on Mapping and Sequencing the Human Genome, where those ideas, combined with an expansion of goals to include genetic mapping, helped to forge a consensus that dedicated genome projects were scientifically worthwhile (National Research Council, 1988).

At Alta, Elbert Branscomb described the state of the art in using flow cytometry and immunofluorescence to detect altered protein products on the surface of red cells. Branscomb later became the computer modeler and one of the architects for the Livermore cosmid map of chromosome 19, now under construction. Tom Caskey reviewed progress on understanding mutations in the HPRT locus, and Sherman Weissman reviewed data on the HLA locus. David Botstein, as always exuding volcanic enthusiasm peppered with sharp humor, speculated about pushing the restriction fragment length polymorphism (RFLP) techniques to their limits—perhaps enough to detect mutations in the range of 10^{-7} per base pair per generation. Unfortunately, this was still shy of what would be needed to detect mutations among the Hiroshima–Nagasaki survivors, unless an unrealistically massive effort were mounted. Ray White talked about applying RFLP methods to the Y chromosomes originating from a single Mormon progenitor of 1850 (who by now has thousands of male descendants) to examine changes in the part of the Y chromosome outside the pseudoautosomal region—a part of the genome where changes should accumulate.

Edwin Southern wound up the scientific session by addressing the gap between cytogenetic detection and molecular methods, and his presence was noted by more than one participant as a moderating influence on the intellectual pyrotechnics. Southern's discussion of measuring uv-induced mutations might be seen to presage the radiation hybrid mapping methods brought to fruition in 1988 by David Cox and Richard Myers, although the two approaches are quite independent in origin.

Michael Gough returned from Alta to Washington to work on the OTA report on detecting heritable mutations. The report had been requested by Congress in anticipation that controversies over Agent Orange, radiation exposure during atmospheric testing in the 1950s, and exposure to mutagenic chemicals might find their way to court, where a neutral assessment of the technical feasibility of detecting mutations would be essential. Gough directed preparation of *Technologies for Detecting Heritable Mutations in Human Beings* until he left OTA in 1985 (U.S. Congress, 1986). Several Alta participants served either as contractors or as advisory panel members for that study. Charles DeLisi, then newly appointed director of the Office of Health and Environmental Research at DOE, read a draft of this report in October 1985, and while reading it first had the idea for a dedicated human genome project (DeLisi, 1988). The Alta meeting is thus the bridge from DOE's traditional interest in detection of mutations to DeLisi's push for a Human Genome Initiative, and provides one of several historical links between genome projects and another massive technical undertaking of the 20th century—the Manhattan project.

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