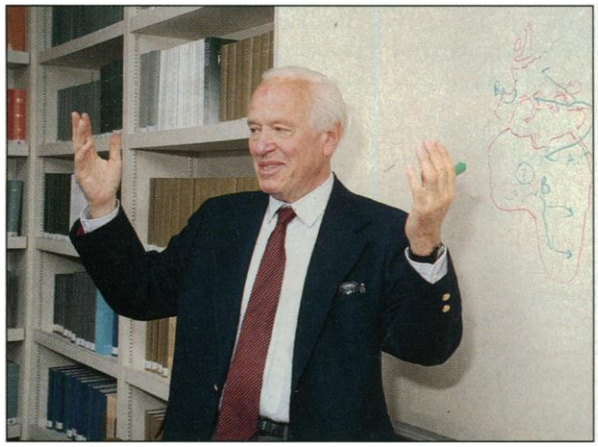
Genetic Diversity Project Tries Again

Geneticists' plans to collect DNA from the world's indigenous peoples were met with opposition, even cries of "racism." Now the scientists are trying hard to win broad support

When a few geneticists first proposed a global effort to survey genetic diversity among the world's peoples 3 years ago, they had high hopes. The project, they said, would yield rich new insights into our species—from the prehistoric movements of peoples, cultures, and languages across the continents to the genetic basis of disease susceptibility. Enthusiasts called it "a cultural obligation to humanity," and the idea quickly caught the imagination of the scientific community: The Human Genome Organization (HUGO) officially endorsed it, anthropologists and medical researchers were eager to help, and funding agencies gave money to develop the idea (*Science*, 21 June 1991, p. 1614).

Then came a sobering dose of reality from the world outside academia. While the organizers debated among themselves the best strategy for collecting DNA samples from diverse population groups, organizations representing the indigenous peoples who would be the main subjects of the survey got wind of the idea—initially through press reports—and went ballistic, accusing the scientists of racism and "genetic colonialism." In Australia, the reaction was so vehement that "it will take 10 years to repair the damage," says John Mathews, director of the Menzies School of Health Research in Darwin. "It confirmed peoples' feelings that they're regarded as experimental animals."



STEVE GLADFELTER/STANFORD UNIVERSITY

Sampling the globe. Stanford's Luca Cavalli-Sforza has spent 40 years studying genetic diversity.

The controversy scared U.S. funding agencies and forced the project organizers to rethink their approach. "I don't think it [initially] crossed anyone's mind that [the project] would be controversial, although it should have," says Henry Greely, a Stanford University lawyer who chairs the ethics group of the project's North American committee. By the end of this year the project's International Executive Committee (IEC), chaired by population geneticist Luca Cavalli-Sforza of Stanford, will reveal the results of this soul-searching when it releases a document presenting its vision of why and how the project should proceed. Some of the measures should help regain the trust of the indigenous peoples, such as local control over the survey and protection of subjects' patent rights. In addition, the United Nations Educational, Scientific and Cultural Organization (UNESCO) in Paris will set up an independent committee to advise the project organizers on ethical issues and try to settle some of the controversy.

The scientific strategy

The Human Genome Diversity Project (HGDP) was the brainchild of Cavalli-Sforza along with Ken Kidd of Yale University and Mary-Claire King, Charles Cantor, and the late Allan Wilson, then all at the University of California, Berkeley. According to the current plan, cell lines and DNA will be prepared from blood, hair, or saliva samples taken from anonymous individuals in different populations, along with a database of the information scientists accumulate about them. The collection will focus on populations that have been geographically isolated or have a distinct culture and language, as these yield more information than genetically admixed urban ones. The material would be available to scientists worldwide for research on human history and biology. Although the cost is not yet fixed, one estimate puts the price tag at $30 million over 5 years.

Beyond establishing the collection, the plan is to begin analyzing the samples during the project's first 5 years. To do so, researchers will compare DNA sequences at a few dozen carefully chosen sites along the genome in individuals from every population. The resulting information—which sequence variations occur at each site in each population, and how prevalent each one is—can be used to infer degrees of relatedness and construct genealogical trees. It will also help answer a different question: How much do individuals vary from the composite "reference" sequence that will emerge from the human genome project?

The plan also emphasizes developing new technologies. Top priority, says genetic anthropologist Ken Weiss of Pennsylvania State University, is to develop improved biochemical methods to copy the full DNA complement of a cell, making it possible to get essentially unlimited amounts of DNA from saliva or hair. This would be vastly simpler and cheaper than the only currently reliable method for preserving DNA indefinitely—making "immortal" cell lines by infecting blood cells with the Epstein-Barr virus—and would allow researchers to sample many more individuals from each population. It would also enable them to salvage DNA from existing collections, such as Weiss's 30-year-old samples from 12,000 individuals in the Amazon region.

Culture clash

These plans may seem innocuous enough, but when researchers first developed them, they misjudged how the idea would be perceived by indigenous groups. In an early planning workshop, groups of mostly North American and European anthropologists sat down and identified a few hundred indigenous groups as relevant to the study. Although not intended as a definitive list, "there was a misperception among some participants that it would be easy to ... create a wish list of interesting populations ... and [the populations] would agree," says Greely. The HGDP organizers soon paid the price for that misperception.

Early in 1993, an organization called the Rural Advancement Foundation International (RAFI), an Ottawa-based group campaigning against Western companies' exploitation of plant species from developing countries, heard about the project and obtained documents—including the list of populations—from the project organizers. They then set alarm bells ringing by alerting many indigenous peoples' organizations.

The reaction was extreme. Groups representing indigenous people were outraged that specific populations were being "targeted"

An African-American Diversity Project

While scientists, funders, and indigenous peoples' groups debate a proposal to survey genetic diversity among the world's populations (see main text), one group may soon have its own genome diversity project—African Americans. Immunogeneticist Georgia Dunston of Howard University in Washington, D.C., is well on her way to launching a project intended to bring African Americans into mainstream genome research. Her mission: to make sure the era of genetic medicine does not pass them by.

She has good reason to be concerned. Virtually all human genome research is done on biological samples from Caucasian donors. That is especially worrisome, as it is known that Africans are the world's most genetically diverse people—as the oldest human population, they have had the most time to accumulate variations in their genetic endowment. And many of these variations will go undetected if only Caucasians are studied.

This lack of knowledge can have severe consequences. One example is the lower success rates of organ transplantation in African American versus Caucasian recipients. The differences are largely due to a higher error rate when tissue-typing African Americans, according to Dunston, whose own research focuses on the histocompatibility (HLA) genes that help determine tissue type. "It has been much more difficult to define HLA type in African Americans than in Caucasians," she says. "Sometimes there were no antibodies or cells to define them."

The key to solving these problems is to have biological material from African Americans available for study. And that is where Dunston's Genomic Research in African-American Pedigrees (G-RAP) project comes in. The idea is to establish a "reference panel" of cell lines from members of large, multigenerational African-American families and make them widely available to biomedical researchers. Dunston and a team of seven colleagues have spent the last 3 years working out a detailed scientific plan for G-RAP and are now applying to several U.S. agencies for funds to launch it.

To find a set of families that accurately represents the genetic diversity of the African-American population at large, they will aim for a collection that reflects the ancestral population of Africans brought to the United States by slave traders. By combing through old shipping records, they hope to glean the information needed to do this: how many people left Africa from which ports, and where they arrived in the United States. Then they plan to sample among families that have lived near the arrival sites in the United States for many generations, and collaborating scientists in Africa will sample at the departure points.

Once the collection is established, its main use will be in mapping genes, such as those which predispose African Americans to diseases such as hypertension, diabetes, and kidney failure. "When we're operating at the level of genetics, there's no magic bullet that works on all groups," Dunston says. "If we want to give all groups the same quality of treatment, we must study all groups. And African Americans must participate in these studies if the knowledge is to be applied to us."

–P.K.

without prior consultation and dubbed the HGDP the "vampire project." Some groups also feared that genetic data could be used against indigenous people, for example, to develop biological weapons specific for a certain population. While this is not scientifically possible, the fear is easy to understand, as genetic theories have been used in this century to support to eugenic ideology, notes anthropologist Weiss. Many were also shocked by the documents' urgings to start the work quickly before endangered groups on the list assimilate or, in a few cases, die out. "The assumption that indigenous people will disappear and their cells will continue helping science for decades is very abhorrent to us," says Rodrigo Contreras of the World Council on Indigenous Peoples (WCIP).

Other objections came from groups whose culture or religion sees giving blood (or DNA) as desecrating the sacredness of the body. And for some, such as Australia's aboriginal people—who have suffered brutal racism over the past century—it was seen as exploitation. Says Mathews: "It's easy for white, middle-class people to see the value of this research. Aboriginal people don't see this. Their health is so poor, for all sorts of reasons, that this [research] seems very remote. Genetics research has been interpreted as just another form of exploitation by white people."

In December 1993, the WCIP invited Greely to its world congress in Guatemala. After a long and emotional debate, the congress unanimously denounced the project. But Contreras says that the council is not totally against such research in principle. "We're not opposed to progress. For centuries indigenous people have contributed to science and medicine, contributions that are not recognized. What upsets us is the behavior of colonization."

The vociferous opposition to the project also raised what is probably the deepest fear about human diversity research: That it is inherently racist and will lead to new gene-based "definitions" of races. While this fear is understandable, says Kidd, all available data contradict it. Genetic variation between members of a population is far greater than that between populations. What's more, populations vary along a geographic continuum, so that neighboring groups are usually genetically indistinguishable, no matter what their ethnicity. Says Cambridge University archaeologist Colin Renfrew: "The very concept of race is in many ways an outdated one. Races can't be defined genetically when you're talking about adjacent populations. A person is culturally Kurdish, not genetically."

HGDP scientists argue adamantly that the project is actually a powerful weapon against racism. With human genome research focused on biological material from Europeans, the rest of humanity is being ignored (see box). "If non-Caucasians aren't studied," says anthropologist Weiss, "they won't benefit as much from biomedical advances." Adds Kidd, "We're not trying to exploit people; we're trying to include them. It's racist to avoid the totality of humans."

Roots of opposition

In some parts of the world, opposition to the HGDP stems from resentment over what is perceived as another sort of genetic exploitation. Some countries are still angered by a project of the International Board for Plant Genetic Resources in the 1970s, when developing countries contributed enthusiastically to an effort that produced a public-domain collection of 125,000 plant germplasm specimens. "Then the war started," says Partha Majumder, a population geneticist at the Indian Statistical Institute in Calcutta and a member of the HGDP International Executive Committee (IEC). Multinational seed companies used some of the strains to pro-

duce hybrids, which they then patented—with no share of the profits going back to the developing world.

"With the atmosphere so charged about plants, imagine how it will be for humans," says Majumder. Indeed, the growing practice of staking proprietary claims on human genes is already hardening suspicions. And opponents of the HGDP really became worried when the U.S. National Institutes of Health and the Centers for Disease Control applied for patents on cell lines from four indigenous people harboring unusual forms of the viruses HTLV-I or -II. HGDP scientists approached by *Science* were uniformly against such practices and vowed to avoid them. But it will be an uphill battle to convince those who have been stung before, says Majumder. "We can shout from the roof that we scientists have no evil intentions, which I firmly believe. But it may be taken with a very large grain of salt by government decision makers."

These fears may lead governments to take action. The Indian government probably will not allow samples collected for the HGDP to leave the country until protocols for collection and use are satisfactorily worked out, according to Majumder, although data on them may be freely available. At this point it remains unclear if any other countries will follow suit. It is an outcome that other HGDP scientists understand, but deeply regret. "If as a general principle most samples aren't available on an open basis, the project will have failed," says Weiss.

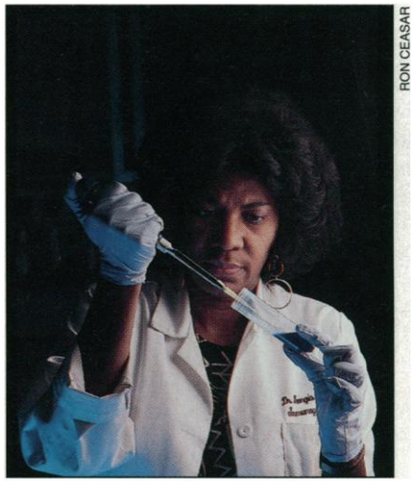
Common ground

The forthcoming IEC document outlines a framework for a plan that researchers hope will counter many of the criticisms leveled at the project. A key feature is for the research to be done as much as possible in the countries or regions where the sampled populations live—Europeans studying Europeans, Africans studying Africans, and so on. Beyond "loose coordination" to ensure that data can be compared globally, says Cavalli-Sforza, "every region should do its own thing," deciding what scientific questions to emphasize, which populations to approach, and how to adapt the ethics rules to local conditions and cultures. So far, regional committees have been set up in North America, South and Central America, Europe, and Africa, while India, China, and Japan have also shown interest.

This opportunity to learn the techniques of genetic research—such as growing white blood cells, preparing DNA, and analyzing DNA markers using the polymerase chain reaction (PCR)—is luring many developing countries to participate in the HGDP. "The new biology must find its way into Africa," says molecular biologist Onesmo ole-MoiYoi, rector of Kenyata University in Nairobi. "This is a way of doing it." But he also points to other reasons. "The motivation is not to be left out. People want to be part of the definition of humanity."

For other indigenous groups, interest in the genetic basis of disease attracts them to the project. Native Americans, for example, have a high incidence of late-onset diabetes, in which genetic factors are known to play a role. And this is one reason why the Euchees and Apaches of Oklahoma have decided to take part in the HGDP, says anthropologist John Moore of the University of Florida, Gainesville. Moore is helping to design a study that will look for clues about the relevant genes and why some Native American groups have an unusual tolerance to high blood sugar. "Many people walk around with no symptoms and feel fine, but ... have a blood chemistry that would put [other people] in the hospital," he says.

But before developing countries will wholeheartedly come on board, guidelines must be drafted to ensure that their rights are protected. UNESCO's International Bioethics Committee (IBC) will hold a hearing next spring where "everyone will be invited to voice their concerns," according to IBC chair Georges Kutukdjian. In parallel, the North American HGDP ethics subcommittee will prepare its own recommendations. And the U.S. National Academy of Sciences, which is likely to do a study next year on how to organize the U.S. effort, will also look at ethical and social questions.



RON CEASAR

Rapport is the key. Howard University's Georgia Dunston, who has conducted genetic studies among African Americans.

One of the most sensitive issues facing this battery of committees is that of informed consent in participating populations. While U.S. rules require written consent from each individual research subject, that is not the best way in all cultures. For example, in many parts of the world, it is crucial to ask the village chief or some other leader first. But while the rules remain to be worked out, one principle is clear, says Greely: Group consent will be sought and respected. "If the chief says no, we won't go looking for individuals from the group who say yes," he says.

Intellectual property rights will also be high on the agenda, although some HGDP scientists see the issue as symbolic, for they doubt that the project will produce patentable findings. They propose setting up a mechanism to ensure that sampled populations would receive a share of royalties on any salable products.

Resolving these ethical issues and deciding in detail how to organize such a mammoth undertaking are now the limiting factors for further progress. Depending on how these are tackled, the U.S. National Science Foundation, which has shown the strongest interest among U.S. funding agencies, could potentially provide funds starting in 1996, according to John Friedlander, head of NSF's physical anthropology section.

The European Union (EU), meanwhile, is already supporting a project within Europe that is giving researchers around the world with a taste of what may be possible on a global scale. The EU is providing $1.2 million to establish a network of 25 labs stretching from Barcelona to Budapest. The researchers involved, who are beginning to collect samples, hope to learn more about the Basque people of the French-Spanish border region, thought to be the most direct descendants of Europe's first post-Neandertal settlers, and about later farming populations that migrated out of Turkey and are the direct ancestors of most present-day Europeans.

In many ways, conditions for the project are optimal in Europe. Its history, languages, and archaeology are extremely well documented, notes network coordinator Alberto Piazza at the University of Turin in Italy. And its easily accessible populations have reacted positively—the "historical sleuthing" has captured the imaginations of many people with no special interest in science or the human genome.

It will be more difficult to capture the imaginations of people in some other parts of the world. But U.S. researchers are encouraged by a recent series of meetings between HGDP scientists and Native American groups, which cleared up a lot of skepticism, says anthropologist Moore. "I think the project will be accepted by Native Americans once we have a chance to explain what we really want to do," he says. "This is the greatest challenge for the diversity project," says geneticist Georgia Dunston of Howard University in Washington, D.C., who has done genetic studies among African Americans. "Success of the project will be very tied to what kind of relationships we as scientists make with the people we get material from."

–Patricia Kahn