times to build up devices, but creating fully 3D structures demands extremely precise alignment of the masks. The Harvard team, led by materials scientist George Whitesides, does away with the need for masks and alignment by defining the shape of the structures with a pattern of capillary channels pressed onto the surface.

The key to the technique is polydimethylsiloxane—otherwise known as silicone rubber. "The big advantage of that polymer is that it will come into tight contact with most surfaces," says team member Rustem Ismagilov. He and his colleagues create patterns of grooves in the surface of the silicone rubber by polymerizing the rubber sheet on a master with ridges on its surface, similar to the way vinyl records are made. Then they press the rubber sheet onto the flat substrate to create closed capillary channels. By passing different chemicals through these capillaries, the researchers can etch away the surface of the substrate or deposit material onto it, following the pattern marked out in the silicone rubber.

The researchers found that they could also deposit material at specific points within a capillary, creating features as small as 3 micrometers, which Ismagilov says does not compare badly with the 0.1 micrometer now possible with photolithography. They relied on laminar flow, a turbulence-free state that develops in fluids under certain conditions. "At the sizes of capillaries we have, it is almost impossible to create a flow that is not laminar," says Ismagilov. As a proof of principle, the researchers exploited laminar flow to deposit silver not across the whole width of the capillary, but just in a narrow strip down the middle.

They introduced the two components of a commercial silver plating solution as two parallel flows in a zigzag-shaped capillary. Because there was no turbulence, the two solutions flowed side-by-side without mixing. They reacted only at their interface, depositing a thin silver thread on the bottom of the capillary. The team went on to use the technique to create a three-electrode microelectrochemical detector inside a capillary: First, they deposited a gold strip on a surface, then etched away a stripe down the middle of it to form two electrodes, and, finally, deposited a silver reference electrode in between the two gold electrodes. Whitesides now has his sights set on making several other types of devices, such as very small detectors and light sources. "I'm hopeful that we can get these systems to lase," he says.

Marc Madou, a microfabrication researcher at the Ohio State University in Columbus, calls the technique "elegant." Both he and Whitesides agree that the technique does not have a great future in high-volume manufacturing because it requires intensive monitoring, for example, of the flows in the capillaries. But, Madou says, it is a "good laboratory tool" for making small experimental devices used in a wide range of research fields, including chemical and biochemical analysis and electrochemistry.

–ALEXANDER HELLEMANS

Alexander Hellemans is a writer in Naples, Italy.

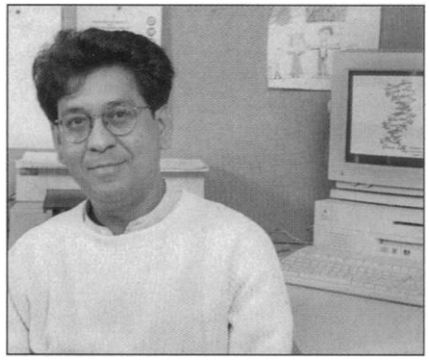
CREDIT: (TOP) DELILAH R. COHN/CUSTOM MEDICAL STOCK PHOTO

HUMAN GENOME

A Good SNP May Be Hard to Find

Over the past 2 years, academic and corporate labs alike have been swept up in a human DNA gold rush. They have eagerly mined the human genome for minute differences between individuals, hoping to use the information to analyze common diseases and create powerful, custom-made drugs. The target: single-base variations in DNA—or single-nucleotide polymorphisms (SNPs)—that occur about once in every 1000 bases of the 3 billion bases in the human genome. Many researchers hope that random collections of these mutations will yield a shortcut to identifying the genes underlying such major diseases as asthma or cancer. But now, findings by a couple of major labs in this field suggest that the payoff of this strategy will not come any time soon, because the most common type of SNPs may not be the most informative.

This cool appraisal comes from two leading teams in SNP research, one headed by human geneticist Aravinda Chakravarti of Case Western Reserve University in Cleveland, Ohio, and the other by Eric Lander, director of the genome center at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. Both groups published reports in the July issue of *Nature Genetics* based on SNP collections they gathered from about 200 different human genes. Their analyses suggest that a popular approach to SNP hunting—comparing entire genomes of just a few individuals to



SNP collector. Chakravarti's group learned that protein-altering SNPs are extremely rare.

ScienceScope

Ethically Acceptable? A presidential ethics panel is ready to endorse a tolerant federal policy on the use of human cells extracted from an embryo (below) or aborted fetus. This week, the National Bioethics Advisory Commission (NBAC) tentatively approved a draft report urging the government to permit both the use of embryonic stem cells and a controversial harvesting technique.

Stem cells are prized because they could be coaxed to develop into almost any body tissue. But Congress has banned federal funding of embryo-harming research due to moral concerns, though the National Institutes of Health interprets the law to mean that grantees may use stem cells from fetuses, or if someone else extracts them from embryos.

NBAC's draft says it should be "ethically acceptable" to use such cells, and to cultivate them from unused "embryos remaining after infertility treatments." Whether Congress will go along with that advice, however, isn't clear.

Property Rights Play Responding to concerns that it's slowing the flow of discoveries to market, the Japanese government may surrender claims to inventions produced by publicly funded research. Proponents hope rules similar to the 1980 U.S. Bayh-Dole law—which surrendered government rights to taxpayer-supported work—will energize Japan's computer and biotech industries.

Japan already gives academic researchers rights to work done under standard grant schemes. But the government still holds varying claims to discoveries made under some major R&D programs, including those run by the Ministry of International Trade and Industry (MITI). Those rights "should be given to the private sector," says Osamu Chisaki, executive director of the Japan Bioindustry Association, which last week pushed the government to relinquish all rights.

MITI officials like the idea and say they will deliver to the Diet a bill seeking to amend relevant laws. But they are still deciding how far it will go.

Contributors: Eliot Marshall and Dennis Normile

find random variations—may miss most of the SNPs that alter the structure of the proteins they encode. Yet these are the SNPs that may directly influence disease risk.

Most SNPs, according to Chakravarti, are not likely to have a direct impact on their protein products. This is because they fall in the estimated 95% "noncoding" area of the genome, or because they behave in a "synonymous" or silent way, coding for the same protein an alternate SNP codes for. Nonsynonymous coding SNPs (cSNPS), in contrast, are very rare in the human gene pool. "There seems to be a strong selection against any change in protein structure. [Most of these changes] have been weeded out in the course of evolution," says Chakravarti.

In addition, Lander's study reports that a significant percentage of the relevant cSNP variants are found mainly in certain subpopulations, such as Asians or African-Americans. "What that tells us," says Leonid Kruglyak, a geneticist at the Fred Hutchinson Cancer Research Center in Seattle, "is that the [nonsynonymous cSNPs] are harder to find in the first place." Chakravarti agrees, adding that "to discover them you'll have to take as large and diverse a sample population as possible."

The scarcity of protein-altering SNPs will also make it difficult to tie them to a specific disease. Lander's study concludes that linking a disease to a very rare gene variant would require thousands of patients, way too many even for state-of-the-art tools for whole genome analysis. At present, says Chakravarti, "The right way to go is to take a set of candidate genes and assess them directly in as many patients as possible" for an association between SNPs and the disease.

This cautionary advice comes as the SNPs stampede is well under way. In January 1998, for instance, Francis Collins, director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health in Bethesda, Maryland, launched a $30 million project to create a collection of some 450 human DNA samples that aims to expand the number of SNPs from a few thousand known today to about 100,000 in the next 3 years. And in April, 10 large drug companies, the Wellcome Trust philanthropy of Britain, and a handful of academic laboratories teamed up to form a nonprofit alliance called the SNP Consortium, or TSC, that will create a SNP archive encompassing some 300,000 SNPs within the next 2 years. Like J. Craig Venter's sequencing factory Celera Genomics in Rockville, Maryland, TSC will collect random data across the entire genome.

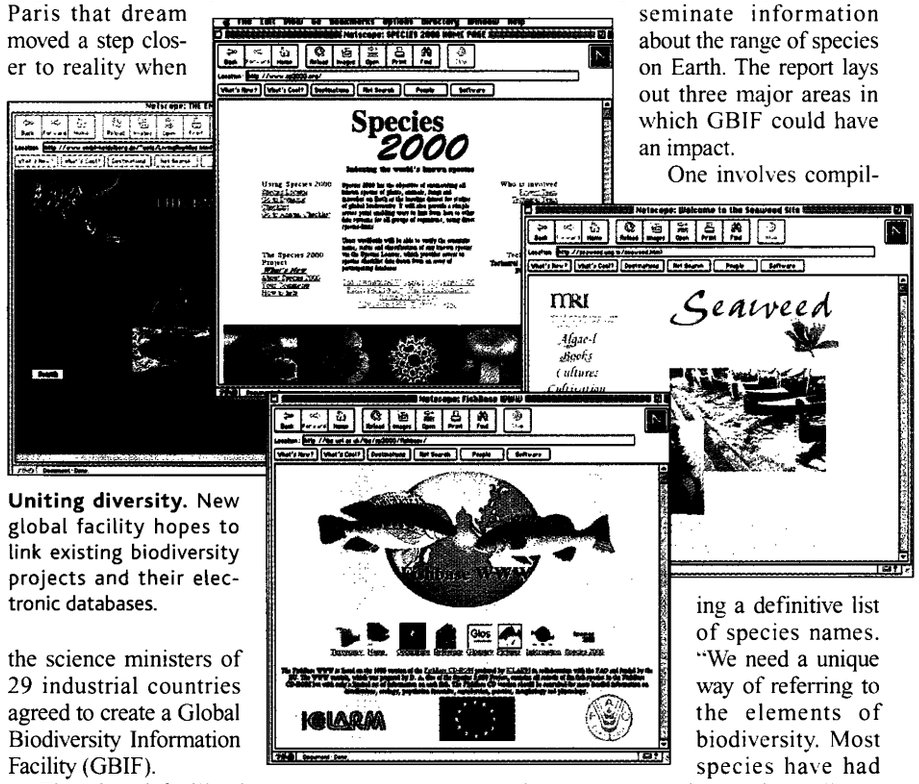
In combination, the gene-focused and random strategies for collecting SNPs should enable scientists to explore the human genome extensively. Celera geneticist Mark Adams says: "I really see [the two approaches] as complementary. The whole-genome strategy will give us a large number of SNPs, both within and outside of genes, and that's a very useful starting point." With this large SNP bonanza just ahead, says Lisa Brooks, program director of the SNP project at NHGRI, research sponsors need to develop new automated technologies that can rapidly "score the genotypes of many individuals." NHGRI is putting money into this area. But Brooks notes that "even a standard screening of, say, 50 candidate genes is still a way off."

–MICHAEL HAGMANN

BIOINFORMATICS

OECD to Set Up Global Facility on Biodiversity

Researchers studying the diversity of life have dreamed of pooling all they know in a single electronic compendium. Last week in Paris that dream moved a step closer to reality when the science ministers of 29 industrial countries agreed to create a Global Biodiversity Information Facility (GBIF).



Uniting diversity. New global facility hopes to link existing biodiversity projects and their electronic databases.

The virtual facility hopes to convert a growing tower of biodiversity Babel, replete with incompatible databases, confusing terminology, and uncatalogued material, into a transparent source of information that is accessible to anyone, anywhere. But before it tackles that challenge, GBIF will have to be transformed from an attractive notion into a real facility with a staff and a budget.

GBIF is the fruit of a 2-year effort by a working group of the Megascience Forum, a body created by the industrialized-country members of the Organization for Economic Cooperation and Development (OECD) to explore possible collaborations in building large scientific facilities. Last week the science ministers agreed it should be renamed the Global Science Forum to better address scientific issues of global significance that do not necessarily involve major construction—such as biodiversity. Last year the parties to the 1992 United Nations Convention on Biological Diversity (CBD) urged OECD to come up with a program like GBIF to give individual countries access to the scientific information they need to carry out the terms of the convention. "GBIF is a very important international undertaking to ensure we can all share openly information about biodiversity," says Neal Lane, science adviser to U.S. President Bill Clinton and vice-chair of last week's meeting.

The new facility incorporates the recommendations of a bioinformatics working group, many of whose members are also leaders of existing efforts to compile and disseminate information about the range of species on Earth. The report lays out three major areas in which GBIF could have an impact.

One involves compiling a definitive list of species names. "We need a unique way of referring to the elements of biodiversity. Most species have had more than one name and some dozens," says Stephen Blackmore, keeper of botany at Britain's Natural History Museum, who served on the bioinformatics working group that proposed GBIF. To produce such a list, GBIF will work closely with Species 2000, an effort just under way to enumerate all known species of plants, animals, fungi, and microbes. "Its endorsement may also help us in obtaining additional funding," says Frank Bisby of the U.K.'s Reading University, who chairs Species 2000.

Another goal is to coordinate the development of new software to link databases that