examine 200 to 400 genetic samples from four populations in Africa, Asia, and the United States. (Previous studies have shown that haplotype patterns differ in part based on migratory histories.)

Enthusiastic about the HapMap's potential to provide medical answers that the full human genome sequence has yet to offer, NIH paved the way, planning a $40 million commitment early this year. Since then, the Canadian government kicked in a little under $10 million and, more recently, the Wellcome Trust Sanger Institute in Hinxton, U.K., about $25 million. Japan, China, and the SNP Consortium, a public-private group seeking single-base differences among genomes, are also adding to the pot.

Work is expected to begin as soon as participants at genome centers in the United States and abroad agree on some ground rules for the project, perhaps the most unwieldy collaboration since the sequencing of the human genome. They have yet to determine, for instance, how data collection will be standardized. Also uncertain is precisely how the map will be structured and how the work will be divvied up.

"We've learned how to find good ways to work together," says David Bentley, head of human genetics at the Sanger Institute. But he notes that unlike the 3 billion bases biologists knew they'd uncover in the genome project, here no one knows quite what to expect.

–JENNIFER COUZIN

WOMEN'S HEALTH

More Questions About Hormone Replacement

Three months after a review panel abruptly stopped a 16,600-woman study of hormone replacement therapy (HRT), a stunned medical community is trying to resolve questions raised by the trial. Last week, several hundred experts and observers gathered at the National Institutes of Health (NIH) in Bethesda, Maryland, to weigh the implications. Most agreed that hormone therapy should not be used to prevent disease. But HRT might still have valid, short-term uses in treating the symptoms of menopause. The risks are not clear, however, nor will they be easy to study, for many acknowledge that large-scale hormone trials might no longer be feasible or ethical.

That point was underscored when the U.K.'s Medical Research Council announced in London at the same time that it was abandoning a similarly ambitious hormone study. The British trial, Women's International Study of Long Duration Oestrogen After Menopause (WISDOM), had planned to enroll up to 22,000 women. It was already struggling to recruit volunteers when the U.S. study of Prempro, a drug combining estrogen and progestin, was halted in July. An interim analysis of the U.S. research, part of NIH's Women's Health Initiative (WHI), had shown that the hormones increased the risk of heart disease, breast cancer, and stroke more than they reduced chances of osteoporosis, bone fractures, and colorectal cancer (*Science*, 19 July, p. 325).

WISDOM's leaders, fighting to keep their trial alive, argued that the benefits might still outweigh the risks for many women. But the Medical Research Council overruled them. Results from the $32 million study, not expected until 2016, were unlikely to differ enough from those of WHI to alter clinical practice, says Oxford University's Ray Fitzpatrick, chair of an international panel that recommended terminating the study.

> "The dilemma now is [how do we decide] who's at too much risk to take hormone replacement therapy?"
>
> —Deborah Grady, UCSF

WHI's outcome, meanwhile, has sown confusion among women and their doctors. NIH organized the workshop in an attempt to clear it up. The befuddlement was due in part to the fact that most women take hormones to counter symptoms of menopause such as hot flashes, which the trial was not designed to evaluate. It examined other health endpoints among women whose average age was 63. Many doctors questioned whether the WHI results applied to women typical of those in their waiting rooms—in their early 50s and just entering menopause. Could the risk of disease attributed to hormone use be lower in a younger cohort?

Shutting down the trial raised broad questions like these, said Deborah Grady of the University of California, San Francisco: "The dilemma now is [how do we decide] who's at too much risk to take hormone replacement therapy?" WHI investigators are poring over 5 years of data to try to identify risk factors. Grady and others cautioned against making assumptions that are not backed up by WHI's data.

The study was halted when 38 per 10,000 women receiving Prempro for a year were diagnosed with invasive breast cancer, compared to 30 in the placebo group. Although this 26% increase is substantial, the risk for an individual woman remains small.

In the future, researchers should "focus on 50 to 59 [year-olds]," was the message from the audience, says Marian Limacher, a WHI investigator at the University of Florida College of Medicine in Gainesville. But she thinks it would be next to impossible to run such a trial: "Who's going to be willing to stay on long-term hormones now?" she asks. Not many, if the aborted WISDOM trial is any indication. Although closely watched trials of HRT to prevent Alzheimer's disease will continue, others—including one on lupus patients—have been abandoned, according to NIH officials.

One of the most vexing questions is whether the risks linked to Prempro use apply to the four other combination HRT products on the market. The National Heart, Lung, and Blood Institute (NHLBI), which funded the WHI study, hopes to find out, although NHLBI's Jacques Rossouw agrees that "women might be a little leery" about enrolling in another hormone trial. Although the Food and Drug Administration is considering relabeling combination hormones to reflect the risks, Janet Woodcock, director of the agency's Center for Drug Evaluation and Research, says differences among product recipes make it "not possible to extrapolate" from Prempro to other medications.

While efforts to sift the results continue, investigators are watching for the next step by Wyeth, Prempro's manufacturer. In July, Wyeth requested access to the study data; NIH agreed to hand the information over. "Once it's released we can't control what they do with it," explained Limacher, who's unhappy that Wyeth will access the data before investigators publish all the findings. But Wyeth vice president Ginger Constantine argued, as Prempro sales plummeted, that "nobody needs science more than us."

–JENNIFER COUZIN AND MARTIN ENSERINK

ANTHROPOLOGY

Going Head-to-Head Over Boas's Data

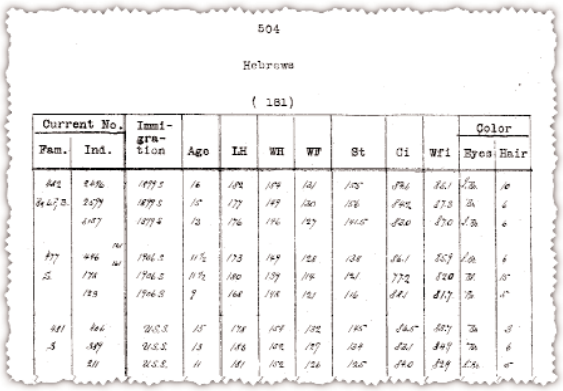
Studying skull dimensions is commonplace in forensics and paleoanthropology. But two new papers offering diametrically opposed analyses of a classic study by Franz Boas suggest that the technique is still controversial for many anthropologists entwined in the ongoing debate over the relation among genes, environment, and race.

Boas, the father of American anthropology, published a study in 1912 challenging the prevailing belief that ironclad genetic rules govern cranial shapes. He took measurements from 13,000 European immigrants and their offspring living in New York comprising seven ethnic groups, the

largest being Hebrews (Jews from Eastern Europe), Bohemians, central Italians, and Sicilians. He compared parent-offspring resemblance in immigrants whose children were born in the United States with those whose children were born in Europe to see whether living in the New World had an effect on skull shape (see graphic).

Using the cephalic index—the ratio of head breadth to head length—Boas found what he saw as a small but significant trend: The U.S.-born children in the four largest groups were more different from their parents than were the foreign-born. Jews, who had "very round head[s]," became more "long-headed," he reported, while long-headed Italians became more short-headed—"so that both approach a uniform type in this country." The study is often cited as evidence that humans can't be pigeonholed in racial categories because their morphology is too malleable.

Rudimentary as his statistical methods may have been, "in general, we conclude that Boas got it right," say Clarence C. Gravlee of the University of Michigan, Ann Arbor, and colleagues in a paper posted online (www.aaanet.org/aa/105-1_gravleeetal.htm) months ahead of its publication in the *American Anthropologist*. The difference in the two groups of offspring, the authors state, is small but "highly significant."


504

Hebrews

(181)

Current No.		Immi-gra-tion	Age	LH	WH	WF	St	Ci	WFi	Color	
Fam.	Ind.									Eyes	Hair
442	2446	1899.5	16	191	154	141	105	806	741	light	10
443	2447	1899.5	15	177	149	130	84	842	873	lt.	6
	2457	1899.5	13	176	146	127	1445	830	870	light	6
477	496	1906.5	11½	173	149	128	138	861	859	light	6
15	174	1906.5	11½	180	139	116	141	772	820	lt.	10
	129	1906.5	9	168	144	121	146	861	847	light	10
481	466	U.S.S.	15	174	149	132	145	846	887	lt.	8
5	469	U.S.S.	13	168	142	127	134	821	849	lt.	6
	511	U.S.S.	11	161	142	126	140	840	889	light	10



Taking their measure. Two teams of researchers have reanalyzed data (*above*) from a classic study by Franz Boas of European immigrants in America—and come to contrasting conclusions.

CREDIT: (BOTTOM) BETTMANN/CORBIS

Wrong, say Corey Sparks of Pennsylvania State University, University Park, and his adviser, Richard Jantz of the University of Tennessee, Knoxville. The divergence in the U.S.-born offspring is "negligible" and the influence of the environment "insignificant," they say in the 7 October *Proceedings of the National Academy of Sciences*. "Uncritical acceptance of [Boas's] findings has resulted in 90 years of misunderstanding about the magnitude of [cranial] plasticity."

Sparks doesn't disagree that Boas found a difference in cranial shape between foreign and domestic-born children. And Gravlee does not quibble with Sparks about the high heritability—and, hence, stability—of the trait. But the two sides disagree on whether the differences, although statistically significant, are also scientifically meaningful.

Sparks says that the differences pale when compared with the much greater variation seen among ethnic groups. "About 99% of the variation [among all the groups studied] is due to ethnic variation and 1% to immigration," Jantz explains. "Boas was right in identifying a small immigration effect," but that has been confirmed in many subsequent studies, he says. "The real value of Boas's work, as reinterpreted by us, is how small that environmental response is."

Henry Harpending of the University of Utah, Salt Lake City, supports Sparks's analysis, arguing that "with samples this large, almost anything can become statistically significant even if it is not worth any attention."

Gravlee, however, insists that the numbers confirm Boas's "overarching conclusion," namely, that "the cephalic index is sensitive to environmental influences and therefore does not serve as a valid marker of racial phylogeny."

The practical impact of the two papers is not clear. Sparks thinks that his analysis will help those who want to use cranial data to study population history, because the Boas study "has been a burr in our bed for 90 years." Indeed, Jantz was a plaintiff in the long-running suit by scientists seek-

ScienceScope

From Classroom to Boardroom President George W. Bush has belatedly nominated eight people for 6-year terms on the National Science Board, the National Science Foundation's governing body, and the list (www.nsf.gov/nsb) contains a few surprises. The biggest surprise is JoAnne Vasquez, who would be the first board member to have made her mark as an elementary school science teacher. Vasquez, now semiretired, is a popular speaker on school reform and a consultant for McGraw Hill Inc. Observers were also struck by the absence of any industrial leaders on the list, which is heavy with engineers and other academics.

The board has been short-handed since May, when a third of its 24 members rotated off. But the new members, nominated 17 October, can't step in until they are vetted and then approved by the Senate, which comes back this month for a short, lame-duck session.

Sea-Floor Science Silenced A federal magistrate has ordered the U.S. National Science Foundation (NSF) to cut short a research cruise off Mexico that was using sound to map the sea floor, backing conservationists who claim that the noise killed several whales (*Science*, 25 October, p. 722). This week's ruling disrupts a $1.6 million international project that was supposed to run through 4 November.

The Center for Biological Diversity (CBD), an Idyllwild, California–based environmental group, asked the court last week to halt the cruise after vacationing whale biologists discovered two dead beaked whales in the Gulf of California on 25 September. Environmentalists believe the deaths are linked to the use of sound-generating devices by the U.S. research vessel *Maurice Ewing*, which was mapping a nearby area. Human-created noise, including military sonar, has been linked to other beaked whale strandings. NSF said there was no clear link in this case, but it did halt the cruise for nearly a week and take steps to avoid whales. But that wasn't enough for the CBD, which successfully argued that the mappers didn't have the requisite U.S. permits—an interpretation disputed by NSF. Says agency spokesperson Curt Supplee: "This is a nightmare of legal ambiguity that will have to be hammered out by the courts."

Contributors: Barbara Casassus, Erica Goldman, Jeffrey Mervis, David Malakoff

ing permission to study Kennewick Man, a 9000-year-old skeleton found in 1996 in Washington state.

Anthropologist Alan Goodman of Hampshire College in Amherst, Massachusetts, agrees with Gravlee that it's risky to rely on cranial data to identify the origins of long-gone populations. "The evidence does suggest that crania do change," he says. "If you want to apply [craniometrics] to Kennewick Man and you know there's instability over a 10-year period, what can you expect over a 9000-year period?" Sparks responds that the instability is largely owing to genetic changes, not plasticity, and that a common ancestor can still be inferred by comparing an ancient skull with a modern one that resembles it.

Heavy media coverage of the Sparks paper prompted the American Anthropological Association to post the Gravlee paper, scheduled for March 2003, on its Web site. The two authors will go head-to-head again in June when the *American Anthropologist* revisits the issue. **–CONSTANCE HOLDEN**

EVOLUTIONARY BIOLOGY

Placentas May Nourish Complexity Studies

It's one of the oldest riddles in evolutionary biology: How does natural selection gradually create an eye, or any complex organ for that matter? The puzzle troubled Charles Darwin, who nevertheless gamely nailed together a ladder of how it might have happened—from photoreceptor cells to highly refined orbits—by drawing examples from living organisms such as mollusks and arthropods. But holes in this progression have persistently bothered evolutionary biologists and left openings that creationists have been only too happy to exploit. Now a team of researchers presents a model system for studying the evolution of complex organs—in this case, the placenta—that Darwin could only dream about.

"Darwin had to use organisms from different classes," explains David Reznick, an evolutionary biologist at the University of California (UC), Riverside, "because there isn't a living group of related organisms that have all the steps for making an eye." And there's no way to put Darwin's solution on firm scientific footing through experiments, Reznick notes, because the organisms in his model are so distantly related to one another.

On page 1018, Reznick and his colleagues propose that guppylike fish in the genus *Poeciliopsis* can solve such problems for the placenta and, by extension, other complex organs. Placentas have evolved independently three times in closely related *Poeciliopsis* species, they report. Other species in the genus lack placentas, and some have partial maternal provisioning by means of tissues that might be precursors of placentas. Thus the fish present the full trajectory of steps involved in the evolution of this organ, Reznick says, allowing researchers to "see what's been added, or what has changed, and eventually identify the genes associated with the evolution of each trait." Adds Stephen Stearns, an evolutionary biologist at Yale University, "Since these placentas have evolved multiple times, we now have a promising model that can be explored and manipulated in the lab—something we've needed for a long time."

Placentas serve as a decent stand-in for eyes and other complex organs such as the heart or kidney whose histories evolutionary biologists have never been able to trace, Reznick and colleagues argue. By definition, complex organs are composites of independently derived features; for instance, the human eye focuses light and also perceives color. In the case of the placenta, the organ provides nutrients for the fetus while simultaneously managing waste products and regulating gas exchanges. Evidence of the intermediate steps for acquiring such organs is missing from the fossil record, enabling creationists to claim they were "created" de novo.

Reznick began to suspect that the poeciliid fish and their placentas could serve as a model for addressing thorny evolutionary questions 15 years ago, while writing a review of live-bearing fish. Earlier this year, one of his co-authors, Mariana Mateos of the Monterey Bay Aquarium Research Institute in Moss Landing, California, developed a phylogenetic tree for *Poeciliopsis*. By combining the tree with Reznick's earlier research and phylogenetic analysis by UC Riverside's Mark Springer, the team now demonstrates that there were three independent origins for placentas in six species of *Poeciliopsis*.



CREDIT: D. REZNICK *ET AL.*

Recurring theme. Placentas (left) that provision embryos (right) have evolved three times in *Poeciliopsis* fish.

The team also estimates the amount of time required for the separation of the poeciliid species. They based their clock on the rate of mutations in the fishes' mitochondrial DNA and incorporated dates of geological events that probably led the species to diverge. The shortest time interval between a poeciliid species with a placenta and its last common ancestor without one was 750,000 years—a period in keeping with the 400,000 years other researchers have calculated for the evolution of the eye. Despite this relatively short period, "it's not a problem for evolution to create this kind of complexity," says Stearns.

Other researchers, such as Günter Wagner, an evolutionary biologist who is also at Yale, caution that Reznick has yet to demonstrate convincingly that the poeciliids' placenta is a complex organ. But even with this caveat, Wagner concedes that the poeciliid model offers evolutionary biologists a rare opportunity: "We should welcome any model, and especially one like this that has several related species with all the variations in the evolution of this trait."

Reznick admits that the poeciliid placenta might not be as sophisticated as the mammalian placenta. But like the evolution of the eye, the evolution of the mammalian placenta is lost in history. "We can't ask how this kind of adaptation evolved with mammals because it only happened once over 100 million years ago," he says. The answer might come instead from small, guppylike fish. **–VIRGINIA MORELL**

PFIESTERIA DEBATE

Is Sugary Toxin the Smoking Gun?

A team of researchers claims to have found more support for the controversial assertion that a toxic microbe called *Pfiesteria* is responsible for massive fish die-offs along the eastern United States. But the new studies, which include the first rough sketch of the toxin, have failed to convince skeptics.

For 10 years, aquatic ecologist JoAnn Burkholder of North Carolina State University in Raleigh has argued that a potent neurotoxin from the dinoflagellate *Pfiesteria* has killed more than a billion fish in East Coast estuaries and sickened lab workers and fishers. However, the toxin has not been identified. This past summer, doubts escalated when researchers at the Virginia Institute of Marine Science (VIMS) in Gloucester Point and other universities reported in two top journals that