known as single-nucleotide polymorphisms. In contrast, some cytogeneticists have taken a more global view of the genomic landscape, mapping out differences in how chromosomes appear under the microscope.

Now two research teams have spotlighted the middle ground, using so-called gene chips to evaluate millions of bases of DNA in a single experiment. The chips—some of the most powerful to date—carry snippets of known genetic material that, when paired up with DNA in a test sample, tell researchers what genetic code is present.

With this wide-ranging view, genomicists Kelly Frazer, David Cox, and their colleagues at Perlegen Sciences in Mountain View, California, have detected insertions and deletions ranging from 200 bases to 10,000 bases in length that differ between chimps and humans, each of which has a genome of about 3 billion bases. Evan Eichler and Devin Locke, geneticists at Case Western Reserve University in Cleveland, Ohio, have studied changes extending about 150,000 bases. "A significant fraction of the variation [between chimps and humans] is present in these [two types of] rearrangements," Frazer reports.

The Perlegen team used chips densely packed with small pieces of DNA, each 25 bases long. The chip is studded with "13 billion unique [pieces]," Cox points out. The researchers assessed the resemblance between the chimp's chromosome 22 and the equivalent human chromosome, 21. They compared 27 million bases, and "much to our surprise, we found around 57 areas of rearrangement between the human and the chimp," says Cox.

There seemed to be no rhyme or reason to the changes; they occurred just as frequently outside coding regions as within. The density of these differences is "a little bit higher than anyone would have predicted," says Eichler. "The implications could be profound," he adds, because such genetic hiccups could disable entire genes, possibly explaining why our closest cousins seem so distant.

Instead of using small bits of DNA, Locke, Eichler, and their colleagues deposited on a chip a series of bacterial artificial chromosomes, each of which contained about 150,000 bases of human DNA. The chip sported almost 2500 sequences covering 360 million bases in all. They compared this DNA to DNA from Asian and African great apes and found 63 chunks that were missing or added. The deletions and insertions they uncovered, which were larger than those picked up by the Perlegen team, tended to be close to large duplicated regions, Locke reported at the meeting, although the researchers aren't sure how to interpret this finding. The frequency of such genetic differences suggests, Frazer says, that "these rearrangements are playing a much bigger role [in evolution] than we expected."

Locke's and Frazer's results come as no surprise to Roy Britten of the California Institute of Technology in Pasadena, who has analyzed the chimp and human genomes using a customized computer program. He compared 779,000 bases of chimp DNA with the sequence of the human genome, both found in the public repository GenBank. Single-base changes accounted for 1.4% of the differences between the human and chimp genomes, and insertions and deletions ranging up to 31 bases long accounted for an additional 3.4%, he reported in the 15 October *Proceedings of the National Academy of Sciences*. Locke's and Frazer's groups didn't commit to new estimates of the similarity between the species, but both agree that the previously accepted 98.5% mark is too high.

Such findings leave researchers eager to scrutinize the full chimp sequence. Japanese, German, South Korean, Taiwanese, and Chinese researchers formalized a chimp genome project in 2001 (*Science*, 23 March 2001, p. 2297); that program recently got a boost when the National Human Genome Research Institute in Bethesda, Maryland, listed the chimp as a high priority for sequencing by its high-throughput centers. The sequence should be ready in mid-2003.

–ELIZABETH PENNISI

PROTECTING HUMAN SUBJECTS

Koski Steps Down After Bumpy Ride

The first director of a federal office created to beef up safety in clinical trials is heading back to academia after running into some bumps within the government and earning mixed reviews from outsiders.

Patient advocate. Greg Koski was "tireless ambassador" for shared responsibility.

Greg Koski, a Harvard anesthesiologist, says his decision to leave after 2 years is not related to the political winds blowing through his office, including a decision this summer to dismantle its advisory committee. But sources say that a lack of support from his bosses might have helped speed his return to academe.

ScienceScope

Pentagon Science Gains A ballooning defense budget is lifting research spending, too. Congress last week approved a $355 billion military spending bill that includes $11.4 billion for science and technology programs in the 2003 fiscal year, which began 1 October. Basic research gets a 7.8% boost to $1.5 billion, and applied studies receive a 12.5% increase to $4.6 billion. Both totals exceed the Bush Administration's request.

The Coalition for National Security Research, a group of universities and science societies, pronounced itself "pleased" by the outcome, which keeps research spending at about 3% of the Pentagon's overall budget. That's a goal backed by numerous government advisers and think tanks. The Pentagon is one of the biggest backers of math, engineering, and computer science research at U.S. universities, but its spending in those areas has lagged over the last decade.

The bill is just the second of 13 annual appropriations measures to clear Congress. The rest of the government is operating on temporary budget measures that freeze spending at current levels.

Separate Partners Congressional negotiators have stripped controversial language on how to manage a $160 million education program from a bill (H.R. 4664) to reauthorize the National Science Foundation (NSF). Legislators last week agreed to eliminate a Senate provision that would have given each state a predetermined amount of money for the fledgling math and science education partnerships program, leaving intact NSF's traditional system of awarding competitive grants through peer review (*Science*, 27 September, p. 2187).

The deletion represents a victory for backers of merit review and for the education lobby, which saw the Senate proposal as a threat to a similar, smaller program run by the Department of Education. "We're very pleased that NSF will be allowed to continue to develop model programs. That's what they do best," says Gerry Wheeler, president of the National Science Teachers Association. The Education Department grants are a better way to serve all U.S. students, he says, adding that the $12.5 million program needs to grow to at least $100 million a year to achieve its goals. Congress must still approve the reauthorization bill, which has been stalled by budget politics (see p. 719).

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tain to intensify interest in a separate lawsuit, in which environmentalists are attempting to block the U.S. Navy from deploying a new sonar that some researchers say could harm whales. Remarkably, the Mexican incident occurred on the same day that more than a dozen beaked whales stranded off the Canary Islands in the eastern Atlantic, following naval exercises conducted by U.S. and Spanish vessels. –DAVID MALAKOFF

ENDOCRINOLOGY

Divorcing Estrogen's Bright and Dark Sides

Despite concerns about the risks of hormone replacement therapy for postmenopausal women, one benefit has not been challenged: It makes bones stronger. Now a study on page 843 suggests that it might be possible to tease apart the various effects of estrogen, maintaining its benefits while reducing its risks. A synthetic hormone has been shown to boost bone strength in mice without affecting reproductive organs.

Estrogen makes women less likely to develop osteoporosis and suffer debilitating fractures. But this boon apparently comes with increased risk of breast cancer, pulmonary embolism, heart attack, and stroke (*Science*, 19 July, p. 325). Reasoning that estrogen's effects on various tissues might be mediated by different cell signaling cascades, a team led by Stavros Manolagas of the University of Arkansas for Medical Sciences in Little Rock has been identifying synthetic hormones that activate only a subset of these pathways.

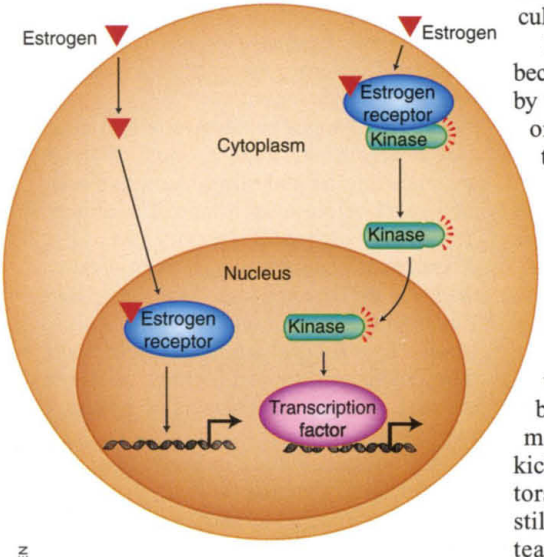

ILLUSTRATION: C. SLAYDEN

Choosing the right message. Synthetic hormones that bypass the traditional estrogen pathway (left) and activate the "nongenotropic" pathway (right) might prevent bone loss without side effects.

Whether such compounds will prove useful in humans remains to be seen, but other researchers and clinicians say the new study is a promising first step. "If it holds up, then it's quite important," says molecular endocrinologist Geoffrey Greene of the University of Chicago. "If compounds like estrogen could be used to maintain bone density with few or no side effects in aging women, that would be huge."

The researchers gave a compound named estren to adult female mice whose ovaries had been removed. As with menopause, ovariectomy curtails estrogen production and eventually leads to a decline in bone density. Estren reversed this change and restored bone strength as effectively as—and in some cases more effectively than—estrogen.

Estren apparently strengthens bones by tinkering with the cellular construction crews that constantly remodel them. At any given time, Manolagas says, there are 5 million to 10 million sites on a human skeleton where cells called osteoclasts dig tiny trenches in the bone that are filled in by bone-forming osteoblasts. After menopause, osteoclasts outpace osteoblasts, making bone more porous and brittle. Manolagas's team found that estren (as well as estrogen) tips the balance in the other direction: Both compounds encourage osteoclasts to self-destruct while prolonging the life of osteoblasts.

Despite their similar effects on bone, estren and estrogen have markedly different effects on the reproductive organs, the team found. In ovariectomized mice, the uterus loses nearly two-thirds of its weight. Estrogen, but not estren, prevents this loss. And whereas estrogen stimulated the growth of cultured breast cancer cells, estren did not.

Manolagas says these differences arise because estren doesn't activate the pathway by which estrogen acts on the reproductive organs. In that pathway—traditionally thought to be the only means for estrogen signaling—the hormone diffuses into the nuclei of cells, where it binds to its receptor and a complex of other proteins that together regulate the transcription of certain genes.

Recently, Manolagas and others have suggested that estrogen can activate a "nongenotropic" pathway, whereby estrogen alters gene expression by means of a biochemical cascade that kicks off when the hormone binds receptors outside the nucleus—an idea that is still controversial. Last year Manolagas's team reported that estrogen's effects on osteoblasts and osteoclasts seem to be mediated by this pathway. The new study suggests that estren activates this pathway but not the traditional one, which would explain its preferential effect on bone.

ScienceScope

Kid Drug Rule Blocked An effort to force companies to test new medications in children has suffered a setback. A federal court in Washington, D.C., last week struck down a 1998 Food and Drug Administration (FDA) rule aimed at developing safe dosing regimens for children. But supporters of the pediatric rule are urging Congress to override the court's order.

The pediatric rule required companies to include children in drug trials before FDA would approve any product likely to be prescribed for children. Prior to the rule, doctors complained that without tests, they had to guess how their small charges would respond to a particular drug. But FDA's move sparked a lawsuit 2 years ago from the Association of American Physicians and Surgeons and two other groups. They argued that Congress hadn't given the agency the power to mandate pediatric testing, and a federal judge agreed. Now, the American Academy of Pediatrics and other organizations are pushing Congress to formally give FDA that power. A vote on the issue could come as early as next month.

Spain's Stem Cell Standoff One of Spain's state governments is hoping to drill a loophole in the nation's restrictive policy on human embryo research. Officials in Andalusia last week announced that they plan a $2 million research center in Seville that will extract human stem cells from embryos that have been frozen for more than 5 years.

The center—to open next year and be led by Bernat Soria of Miguel Hernández University in Alicante—aims to sidestep a 1988 ban on research involving "viable" embryos. Since that vaguely worded law also forbids implanting embryos that are more than 5 years old, Andalusian officials argue that such embryos are not viable and therefore are accessible to researchers.

It's not clear if federal officials will agree. Health minister Ana Pastor, who has criticized stem cell research advocates, has called a "technical meeting" with Soria later this month. If she tries to scuttle the center, Andalusian officials could appeal to Spain's high court, notes geneticist Josep Egozcue of the Autonomous University of Barcelona. But public pressure to approve the center will be enormous, he predicts, noting that patient groups recently collected 1.3 million signatures on a petition calling for the government to back stem cell studies.

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