Genome Project Under Way, at Last

With many of the major questions settled, NIH is trying to figure out exactly what the new genome project will entail

AFTER YEARS OF DEBATE over "should we or shouldn't we?" National Institutes of Health officials, with the help of 12 eminent biologists, are now rolling up their sleeves and sorting out just what the human genome project will entail. To the newly constituted Program Advisory Committee on the Human Genome, which met in Bethesda last week for the first time, there seemed to be a sense of relief at getting down to work, at last.

The central task for the 12-member committee, headed by Norton Zinder of Rockefeller University, is to define the scope of the project, or, as NIH director James B. Wyngaarden put it, "the boundary between what would be going on anyway and what is different." On a practical level, the question is what NIH will do with its burgeoning funds, $28 million for fiscal year 1989, with $100 million proposed for 1990.

There was little dissent among the group, which is not surprising, considering that many of the members slogged through these same issues earlier when they served on committees for the National Academy of Sciences (NAS), the Office of Technology Assessment, and the Department of Energy. Said Zinder: "Those reports all had an air of abstraction. This time, what we say may actually have consequences."

The committee has to report to Congress in about a year. Meanwhile, Wyngaarden is seeking to elevate the new Office for Human Genome Research to center status, giving it more autonomy and enabling it to dispense grants, which now must go through the National Institute of General Medical Sciences (NIGMS).

It was almost a year ago that Wyngaarden announced the creation of a special, high-priority genome office within the NIH director's office, thereby ending speculation on whether NIH or DOE would lead the effort. Since then Wyngaarden has been putting things in place, recruiting Nobel laureate James Watson to head the office and appointing the advisory committee that will guide the effort.

At the outset of last week's meeting, Watson reminded the group that to reach their not-so-modest objective—as he described it, "to find out what being human is"—will entail not research as usual but the creation of a resource, which he likened to building a giant accelerator. But unlike an accelerator, said Watson, "it will generate important results in 5 years. We don't have to wait 'til the end. We don't need the last base to say we are done."

He envisions a 15-year program, beginning with genetic and physical mapping and technology development and gradually phasing in sequencing. Watson predicted that a detailed genetic map of all the human chromosomes, which will help to locate disease genes, could be finished within 5 years, "if someone says, 'get it done.' I will push people probably harder than they want. I am impatient."

> ***"The sequence is just a punctuation point in this endless project in human biology."***
>
> *—Norton Zinder*

What sort of research will fall under the rubric of the genome project? While the ultimate goal is the map and sequence of the human genome, the committee agreed that the project should begin with an emphasis on other complex genomes such as *Escherichia coli*, yeast, nematode, *Drosophila*, and perhaps mouse and the plant, *Arabadopsis*.

It was this comparative genetics approach, outlined about a year ago by the NAS panel, that brought consensus among the more gung-ho advocates of the project, who wanted to plunge in with an all-out effort to sequence the human genome, and those who saw it as a colossal waste of money that would yield a sequence but not the ability to understand it.

The reason this approach makes scientific sense, said David Botstein of Genentech, is evolutionary conservatism. "It is a tremendous fortune that evolution has used the same parts over and over. When we encounter a human gene we are likely to understand it because we have seen something like it in an organism we can study."

Phillip Sharp of the Massachusetts Institute of Technology warned against being too dogmatic in this focus. "We should have a major emphasis on those organisms but not build a wall around them," he said, adding that rigidity might discourage innovative researchers who want to work on model systems out of the mainstream.

The flip side, however, as Maynard Olson of Washington University pointed out, is that "there is a tremendous potential out there to diffuse a tremendous amount of money. There are lots of meritorious organisms, and we will probably have to err on the side of rigidity."

The committee also endorsed the concept, first proposed by Olson to the NAS committee, that the guiding principle should be whether the work will bring a three- to fivefold improvement in either knowledge or technology, such as sequencing speed. When Olson first broached the idea, the best compromise he could broker among the NAS panel was a five- to tenfold improvement. That this new committee will now settle for a more modest improvement, noted Olson, is a grudging acknowledgment of just how hard the task ahead will be.

One of the trickier questions the project will face is how to balance the public's desire for progress on genetic diseases with the committee's emphasis on building a tool and not necessarily applying it. Victor McKusick of Johns Hopkins University suggested some attention, at least, to searching for the genes of the "biggies"—genetic diseases like cystic fibrosis and Huntington's.

There is already a huge amount of money out there for genetic diseases, objected Botstein, who added that the "tool business is always given short shrift." His view ultimately held sway. "We are looking at the production of a set of tools that will allow human geneticists to do what they want. We are the Cray, if you like. We don't write software for your particular application."

Such a focus, however, might require a herculean public relations task, as Olson noted: "It will be hard to explain to the public why efforts to deal with diseases are not part of this multibillion dollar project."

Nancy Wexler of Columbia University came up with a compromise, pointing out

that at least some of the effort to develop new technologies can be done in conjunction with research on human diseases. She cited, for example, the powerful physical mapping technique, pulsed field gel electrophoresis, developed by Charles Cantor and his colleagues at Columbia University. The technique had never been tried on human DNA until Wexler's group offered them DNA from chromosome 4, the location of the still-elusive Huntington's disease gene.

The critical organizational question the committee grappled with was whether the new program should establish research centers and, perhaps more important, fund their construction. The answer is, yes, the committee concluded, if the program's tight deadlines and ambitious goals are to be met.

"Realistically, that is the only way programmatic progress will be made," said Olson, who added that the grants funded by NIGMS this year are probably the best the group will see, "but they simply don't add up to a program." And convincing universities to take on a new center, said Watson, will "require the carrot of new space"; thus, the need for construction funds.

These centers, which might focus on physical mapping of the nematode, for example, should not be created de novo, the committee agreed, but should grow up around the best labs in the country already doing this work. The problem is, there just aren't that many of those embryonic centers around, which is a stark reminder of just how few experts there are at this stage.

The challenge, the committee members agreed, will be to create true intellectual centers and not just paper entities. As Bruce Alberts of the University of California asked: "How do you establish centers without the inertia we fear will develop and the wasted resources?"

Committee chairman Zinder established a working group to look at the number and size of centers, their areas of expertise, and other questions. Zinder also set up working groups on training, databases, and ethics.

Ethics will be a central concern of the genome office, said Watson."Some very real dilemmas exist already about the privacy of DNA. The problems are with us now, independent of the genome program, but they will be associated with it. We should devote real money to discussing these issues. People are afraid of genetic knowledge instead of seeing it as an opportunity."

The committee meets again in June, but the working groups may be called on before then as Watson and Wyngaarden prepare for this spring's budget hearings, when Congress will undoubtedly want to know what is in store for the year ahead.

■ LESLIE ROBERTS

Pruning the Thickets of Cosmic Speculation

Cosmology currently suffers from too much theory and not enough data; the new Center for Particle Astrophysics could help

FOR MORE THAN A DECADE now, the nascent field of particle astrophysics has grown like a garden gone wild. Cosmic strings, cosmic inflation, particles of invisible "dark matter"—whole thickets of speculation have sprung up around the events of the Big Bang as physicists and astronomers have struggled to understand how the dynamics of particles *then* could have shaped the universe we see *now*.

During the next 2 or 3 years, however, that garden is due for a severe pruning. Researchers are beginning to put cosmological speculations to the test with experiments in a variety of areas, notably dark matter, gravity waves, and the cosmic background radiation.

Perhaps most significantly, these experimental efforts have now received official recognition from the National Science Foundation in the form of a Center for Particle Astrophysics at the University of California, Berkeley. With 25 member scientists and a budget of $10.6 million over the next 5 years, the Berkeley center will try to facilitate and coordinate as many of the new projects as possible. Moreover, despite the inevitable concerns about siphoning off funds from *non*-center projects, the center has generally been greeted with enthusiasm: "It's a very healthy step," says Princeton University's David Spergel, who was a principal in an unsuccessful bid to locate a similar center at Princeton. "It recognizes the emergence of a subfield and it emphasizes *data*."

At least initially, says director Bernard Sadoulet, the center will focus on the problem of dark matter, which comprises up to 90% of the mass in the universe and which is detectable only by its gravitational effects on galaxies and clusters of galaxies.

Current conventional wisdom has it that dark matter can most plausibly be explained as a universe-wide haze of elementary particles left over from the Big Bang. One reason for thinking so is that the physicists' theories of grand unification and supersymmetry predict a variety of heavy neutrinos, "axions," and "photinos" that would serve quite nicely. Each of these hypothetical particles would possess a small mass, so as to produce the gravitational effects; and each of them would interact very weakly with ordinary matter, so as to remain invisible. (Thus their generic name: Weakly Interacting, Massive Particles, or WIMPs.) Another reason is that computer models suggest that the gravitational dynamics of such a particle haze would produce a distribution of galaxies and clusters in the universe very much like the one we see. All that is required is that the particles come out of the Big Bang moving much slower than the speed of light—or in a word, that the dark matter be "cold."

Plausible or not, however, this is precisely the kind of model-making that Sadoulet and his colleagues at the Berkeley center want to test. They are currently planning several lines of attack. Some highlights:

■ **Direct detection of dark matter particles.** This is the center's highest priority and most formidable technological challenge, says Sadoulet. Even with an estimated flux of roughly 1 million dark matter particles per square centimeter per second, a 1-kilogram detector would experience roughly one event per day. Moreover, each event would only deposit some 1000 electron

Lawrence Berkeley Laboratory

Bernard Sadoulet. *Dark matter is the center's highest priority and toughest challenge.*