Watson May Head Genome Office

By establishing a special genome office and recruiting an eminent scientist to run it, NIH has assumed the lead in the ambitious new program to map and sequence the human genome

JAMES Watson, who shared the 1962 Nobel Prize with Francis Crick for elucidating the double helical structure of DNA, has been asked to head the new Office of Human Genome Research at the National Institutes of Health (NIH). If Watson agrees to take the helm, as he is expected to do, and if Congress gives NIH the $28 million for genome research that it has requested for fiscal year 1989, then NIH will become the de facto lead agency in biology's biggest new project: the effort to map and sequence the human genome.

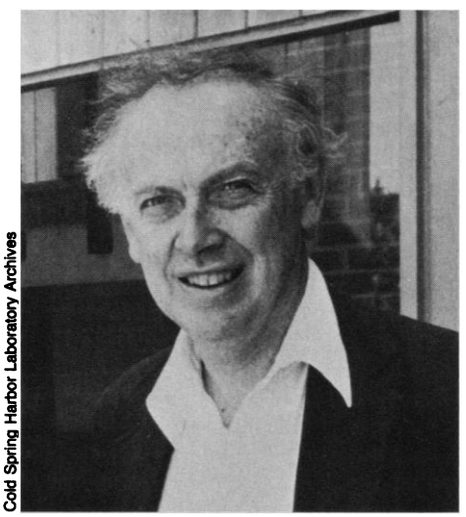
Watson is reportedly eager to take on the post as associate director for genome research but first must resolve several ongoing projects at Cold Spring Harbor Laboratory, where he has been director since 1968. The NIH slot would be part time, allowing Watson to remain at Cold Spring Harbor. He has promised a decision by mid-May.

When NIH director James B. Wyngaarden announced in February the creation of the new genome office within the NIH director's office, many in the biological community breathed a collective sigh of relief. In the 2 years since the estimated $3-billion, 15-year project was first proposed, NIH had endorsed it only coolly. By contrast, the Department of Energy (DOE), where the idea first originated, had been lobbying hard for the lead role. Despite DOE's track record in managing large projects and in technology development—the linchpin of the genome effort—many biologists are leery of the quality of DOE's peer review and feel more comfortable with NIH.

NIH's concerns were twofold. First, at the scale envisioned for the project—which would involve mapping the location of all the genes and then painstakingly determining the exact sequence of all, or at least most, of the 3 billion nucleotide bases that make up the human genetic complement—the project was an intellectual departure from investigator-initiated work that NIH has traditionally supported. Moreover, it threatened to siphon off funds from other areas of biological research. "Our community was quite apprehensive," notes Wyngaarden.

Establishing the new office is "an intellectual and scientific change of course," acknowledges Wyngaarden, "or at least a compass course adjustment."

"I welcome NIH's involvement," says Maynard Olson of Washington University, one of a dozen or so scientists who have been advising the director. "Most of the experience in this area lies in labs NIH has funded." All along, he says, "the concern was not big science but bad science." NIH will allay those fears. Says Olson: "People are confident in NIH."



Cold Spring Harbor Laboratory Archives

James Watson: *An undeniable appeal to "starting with the double helix and going up to the double helical structure of man."*

What nudged NIH off the fence was a clear signal that both Congress and the Administration wanted NIH to assume a prominent role in the genome project, says Wyngaarden. For fiscal year 1988 Congress appropriated $17.2 million specifically for genome activities at NIH (Wyngaarden requested $50 million, but not as a priority item). And for 1989, NIH's request for $28 million has cleared the White House and the Office of Management and Budget.

Wyngaarden was also swayed by the lobbying of several prominent scientists, including Watson, who clearly wanted NIH to take the lead yet wanted to ensure that the project did not compete for funds with other NIH programs. Locating the project within the director's office, as Watson suggested, solves that problem, at least to some extent. Wyngaarden has other reasons as well: "I wanted to give it maximum visibility to give it maximum appeal to someone like Jim Watson."

While Watson will not comment on his decision, he does admit that there is an undeniable appeal to "starting with the double helix and going up to the double helical structure of man."

Watson defines the task of the new office, which should be functioning within a month or two, simply: "To see that the project is well organized and done as fast as possible at a reasonable cost, without taking money from good science." Wyngaarden sees the budget climbing to about $200 million a year within 4 or 5 years.

For the time being, the office will not have a grant-giving role; rather, it will set priorities and monitor funding. All grant proposals will be handled through the traditional peer-review mechanisms within the Institute of General Medical Sciences and perhaps other institutes. But if the budget continues to grow, the office could be elevated to division status with its own research budget and grant-dispensing mechanisms.

A program advisory committee, composed of a dozen or so scientists and perhaps ethicists and public representatives as well, is now being assembled. Both DOE and NIH have agreed to share at least some scientific members of their respective advisory committees to ensure coordination.

Meanwhile, the genome project itself is being recast in a more realistic light. "There is a new air of caution," says Olson. Some of the hype and overly optimistic claims made by the project's early advocates have given way to a more sober appraisal of just what it will take to get the job done. "The project was misformulated in the early stages of the debate," says Olson. "The real problem is we don't know how to do this at all. We will need to develop a new field."

This reappraisal is apparent in the 5-year strategy for NIH's new genome office, formulated by an ad hoc advisory committee that Wyngaarden convened in February.

The immediate goal, on which there was unanimous agreement, says Watson, is a fine-resolution genetic linkage map of the human genome, with markers spaced 1 centiMorgan apart on all the chromosomes.

Such a map, which will speed the search for disease genes, represents a tenfold improvement over the current genetic map—"an achievable but fairly horrendous increase," says Olson. The benefits, however, are clear. "If your child has cystic fibrosis, then there is some urgency," notes Watson. "If we can get the mapping done in 4 years instead of 6, it seems to me that this is progress."

For the physical maps, which involve actually lining up fragments of DNA in the order they appear along the chromosomes, the goal has been scaled back from mapping the entire human genome within a few years to mapping one or two small human chromosomes within 5 years.

For areas other than genetic mapping, the primary emphasis will be on technology development, says Wyngaarden: new technologies for physical mapping, sequencing, and information-handling. Massive sequencing will not start for at least 5 years.

A key question the ad hoc committee grappled with, and that seems likely to plague the soon-to-be-established program advisory committee as well, is how to distinguish this work from other projects in molecular genetics. Borrowing from the recent National Academy of Sciences (NAS) report, the committee recommended that NIH support work that, as a rule of thumb, offers a five- to tenfold improvement over existing capabilities, whether it be the sequencing rate, the size of a clone, or the resolution of a map.

By establishing this special office and lobbying for a boost in funds, NIH has wrestled the lead away from DOE, which has a focused, but smaller, program, now funded at $18 million. "I don't see this as an important turf battle," says Wyngaarden. "What really determines how much we all do is funding."

Whether Congress will feel the need to legislatively designate a lead agency remains to be seen. In its report the NAS pushed for a single agency to direct the project; the Office of Technology Assessment argued against it, recommending instead an interagency task force.

"I don't think there need be a lead agency," says Wyngaarden, "but if there is one, NIH is the only logical place for it. This isn't primarily a hardware and information project. The reason for doing this is to extract the biological information in the genome."

Watson, however, thinks a lead agency is essential. "Who are you accountable to without a lead agency?" he asks. At a recent congressional hearing Watson recommended that "NIH should be the primary dispenser of the vast majority of funds—80% of the funds." His arguments have proved persuasive in the past. ■ **LESLIE ROBERTS**

Brain Graft Puzzles

During the recent rush to implant adrenal gland tissue into the brains of Parkinson's disease patients, the focus of attention, quite naturally, has been on the hoped-for improvement in symptoms (Research News, 22 April, p. 390). Amid all this attention on the therapeutic effects of the procedure, there has frequently been observed an epiphenomenon that, until now, has been unreported, except in a very anecdotal manner. Specifically, many patients appear to experience a series of unusual and unexpected behavioral changes that begin immediately after surgery and may persist for several months.

"Everyone has seen these behavioral changes in at least one of their patients," says Caroline Tanner of Rush Medical Center, Chicago. "Some of the changes are quite subtle, and you have to look carefully for them." In collaboration with Harold Klawans and his colleagues at Rush Medical Center, Tanner has made a systematic study of this phenomenon, which she described at the recent meetings of the American Academy of Neurology.

The behavioral effects observed in the Chicago patients fall in five categories. First, patients have a significantly reduced need for analgesics immediately following surgery. "This is not just because they are drowsy," says Tanner. "It is a real change in pain threshold." Second, about 3 days after surgery patients' sleep patterns change for about 3 or 4 days. "They tend to fall asleep often during the day, not through an increased lethargy, but simply spending more time asleep."

Third, and most intriguing says Tanner, are delusions of various sorts, ranging from simple to flamboyant. For instance, one man, a farmer, was convinced that a farm store was attached to the hospital. In another case, a woman described herself as floating on a lake, whereas, of course, she was sitting on a hospital bed. Another man was convinced that appliance salesmen were visiting patients in their rooms, persuading them to buy things, from which the hospital was getting a cut. He was very angry about the whole thing. "In each case the patients' behavior was quite appropriate, and unless you touched on the topic of the delusion, you wouldn't be aware that anything was amiss," says Tanner. Later, when the delusions had passed, patients often remembered "knowing" that they had been true, but also "knowing" at the same time that they were not.

Fourth, some patients experienced personality change, including disinhibition and mania, sometimes shifting from a reserved, conservative personality to being exuberantly outgoing. And fifth, several patients experienced visual and auditory hallucinations. Now, it is true that Parkinson's disease patients sometimes have hallucinations, mood changes, and other behavioral phenomena when they are treated with the standard drug, levodopa. But, as Tanner points out, the patients in her study had been under observation for a very long time, and the symptoms that emerged after surgery were novel for each of them. In addition, some of the behavioral effects are qualitatively different from those associated with levodopa.

Anecdotal reports from other medical centers match the Chicago experience to varying degrees. For instance, Abraham Lieberman at New York University Medical Center told *Science* that out of 12 patients, he had noticed some effects in a few patients, and strikingly so in one. And George Allen's group at Vanderbilt University has seen "confusional" effects in some of the older patients, but not in younger patients. Tanner notes that the criteria used by the different transplant groups for selecting patients—severity of symptoms, age, and so on—may influence the degree of postoperative behavioral changes that develop.

Although patients who undergo brain surgery as extensive as that in adrenal implantation sometimes experience some of the phenomena that Tanner describes, it is rare and much less developed. The changes may therefore be related in some way to injury specifically to the caudate, which is where the implant is inserted, or to the adrenal implant itself, which is packed with various neurotransmitters, including catecholamines, opioid peptides (enkephalins and endorphins), and probably some steroids too. However, the Chicago group was unable to find any correlation between changes in cerebrospinal fluid levels of these chemicals and the changed behaviors. Nor was there a correlation between the behavioral effects and any modification of parkinsonian symptoms. A direct pharmacological effect of the neurotransmitters therefore looks unlikely. ■ **ROGER LEWIN**