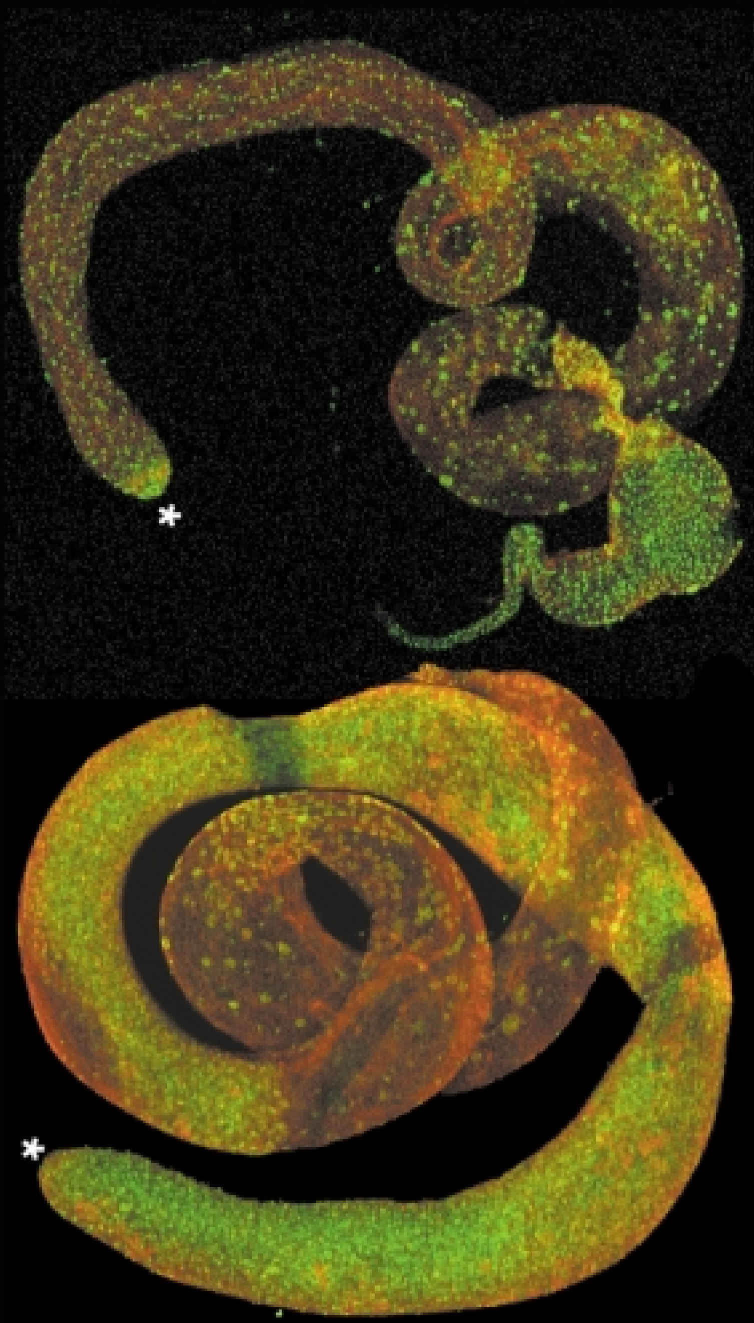

THE DIRECTOR'S REPORT

"...THIS INSTITUTION AND THE DEPARTMENT OF EMBRYOLOGY HAVE BEEN STRIVING TO DECIPHER GENE STRUCTURE AND FUNCTION FOR MOST OF THE LAST 100 YEARS."

Genetic studies that focus on entire genomes, a field now known as genomics, are engaging widespread public interest in biological research. Genomics strives to discover all of an organism's genes, and to determine their chromosomal location, structure, regulation, expression, and function. Making this information publicly available in large databases allows biologists to undertake powerful new approaches to previously intractable biological phenomena. A collection of technologies, including large-scale DNA sequencing, software development, and the increasing use of automation, are greatly accelerating the speed and capabilities of gene-focused studies, driving this research toward a "postgenomic" era. This year alone, the gene-rich portion of the fruit fly *(Drosophila)* genome was sequenced, and the nearly finished human genome sequence will be published shortly. These developments unquestionably open many new opportunities for biological research and cause us to rejoice at our good fortune to be working as biologists at this particular point in history.

Genomic research is frequently viewed by the public, and even in some scientific quarters, as a relatively new development. In reality, though, this institution and the Department of Embryology have been striving to decipher gene structure and function for most of the last 100 years. The Carnegie Institution became involved in *Drosophila* genomics almost 90 years ago through its support of researchers in the Thomas H. Morgan laboratory at Columbia University. The intellectual program of classical genetics, as reflected in Morgan's research, set many of the same goals of gene discovery, mapping, and analysis that are today being realized using DNA sequences. Led by Calvin Bridges, then a Carnegie employee, *Drosophila* genomic information was compiled into some of the first genome databases and distributed to the public as Carnegie Institution of Washington (CIW) publications. Detailed summaries of genes on the X-chromosomes (1915) and on chromosomes 2 (1919) and 3 (1927) were released in CIW publications numbers 213, 278, and 327, respectively. In 1944, following the first detailed physical mapping of the genome using polytene chromosomes—also

Left: This image shows photomicrographs of two *Drosophila* testes. The Matunis lab is searching for molecules that regulate stem cells by genetically removing candidate signaling molecules from testis tissue and examining any corresponding change in the number of stem cells. The smaller testis is a wild-type control with just a few stem cells at the apical end. In the larger testis, the STAT signaling has been overinduced, resulting in the production of thousands of cells with stem-cell characteristics; these appear as bright green. This result suggests that Jak-Stat signaling instructs stem-cell fate, rather than maintaining cell viability.

accomplished by Bridges—enhanced databases linking genes to specific chromosomal sites were distributed in CIW publication number 552. Later, in 1967, Dan Lindley and E. H. Grell released a further update as CIW publication 627. These later two works served for 50 years as indispensable preelectronic *Drosophila* Web sites with countless daily "hits" by active researchers.

Identifying genes and describing their activity is unquestionably important, but analyzing gene function remains the critical element in gene-centered biology. Research from this department, on several occasions, has accelerated this aspect of genomic research. Classically, the genes required for a particular physiological process are discovered by identifying mutations that prevent the process from occurring normally. To complete this "forward" genetic approach, it is necessary to decipher the molecular identities of the altered genes. In contrast, by first purifying genes, transcribing them in vitro, and assessing the effects of chemically produced mutations, Don Brown's group forged one of the original templates for an alternative or "reverse genetic" approach to understanding gene function. Today, with a plethora of genes defined only by their DNA sequence, reverse genetics is on its way to becoming the norm.

To understand what roles genes play in a multicellular organism, genetically altered animals must be constructed in which the activity of individual genes can be experimentally controlled or eliminated. This task has been facilitated by current and former department Staff Members who developed methods for introducing altered DNA molecules into the genomes of *Drosophila* and the nematode *Caenorhabditis*. Creating methods to mutagenize the genomes of *Arabidopsis* or *Drosophila* using transposable elements has also helped. In the case of the fruit fly, this latter approach is continuing under the leadership of Dr. Robert Levis, who joined the department this year as a research scientist. Working with collaborators at the University of California at Berkeley (including former Staff Member Gerry Rubin), at the Salk Institute (including former postdoctoral fellow Gary Karpen), and at the Baylor College of Medicine,

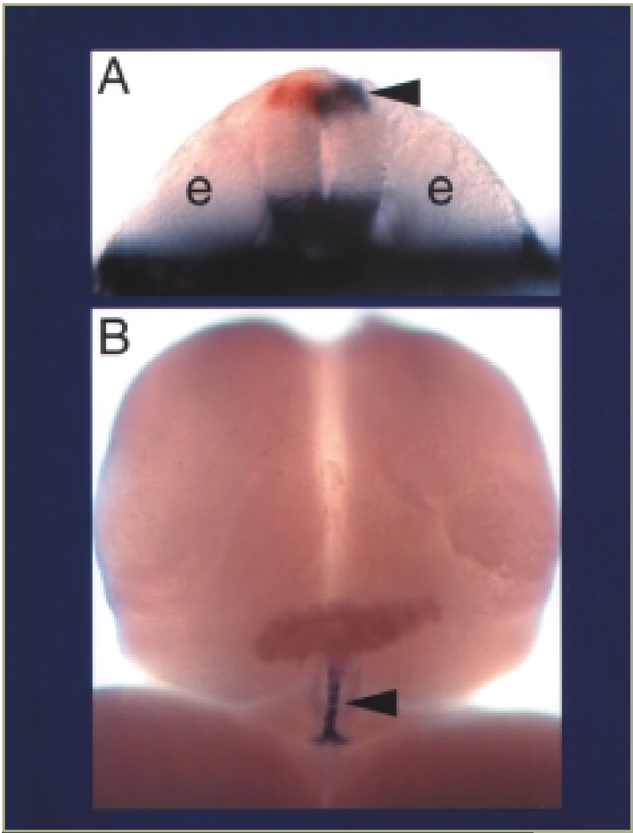

Fig. 1. The Halpern lab uses genetic approaches in the zebrafish to study how signaling pathways regulate the differentiation and patterning of the central nervous system. The top image shows a frontal view of a zebrafish embryo, with the eyes indicated by (e). The *floating head* gene is expressed on both sides of the forebrain, in the pineal organ (red). However, the *pitx2* gene, while expressed on both sides of the brain ventrally, is only expressed on the left side dorsally (arrowhead). In the adult (bottom image), *floating head* expression persists in the stalk of the pineal organ (arrowhead), which in a normal fish typically emerges from the dorsal diencephalon at left to medial position. This work is providing new insights into the anatomical and functional differences between the left and right sides of the brain.

Levis expects to identify mutations that inactivate or alter more than half of the 13,600 estimated *Drosophila* genes within the next two years. Additionally, Staff Member Marnie Halpern's group continues to generate zebrafish in which groups of adjacent genes throughout the genome have been deleted. The strains produced by both the *Drosophila* and zebrafish projects help researchers study gene function, and they are being provided to public stock centers for distribution.

One of the most versatile new methods for discovering what genes do was developed recently by Staff Member Andy Fire in collaboration with Dr. Craig Mello of the University of Massachusetts, Amherst. Their method of "RNA interference" allows gene transcripts to be inactivated within individual cells or in whole invertebrate organisms following uptake of complementary double-stranded RNA. The discovery by Fire and postdoc Lisa Timmons that a gene's activity can be shut down when worms simply ingest bacteria containing the appropriate double-stranded RNA has made it possible to use RNAi to functionally screen large numbers of *C. elegans* genes. Several laboratories and start-up companies are currently racing to study all of the known *Caenorhabditis* genes using this method. Several other departmental members, including graduate student Kan Cao and Staff Member Yixian Zheng, are using RNAi to downregulate specific *Drosophila* genes in tissue culture cells. Another group, led by Staff Associate Jim Wilhelm, is preparing to expand this approach so that the entire roster of fruit-fly genes can be scanned for their effects on any cellular process of interest. In addition to its speed and simplicity, RNAi promises to allow experimenters to shut off multiple genes located in different chromosomes simultaneously. This has been difficult to do using traditional methods and greatly facilitates the discovery of gene interactions and pathways.

The need for detailed information on genome structure and for tediously acquired mutant collections has caused biologists to focus on a relatively small number of "model" organisms. These include flies, worms, mice, zebrafish, and yeast. One unfortunate side effect of this trend has been to discourage gene-based research into problems that are better studied in species lying outside this narrow group. However, advancing genomic technology is now creating opportunities for gene-based studies within nontraditional organisms. Staff Associate Alejandro Sánchez and postdoc Phil Newmark have taken the flatworm planaria, an organism that lacked modern genomic resources, and in just three years have generated the tools needed for sophisticated genetic studies, including genome-wide surveys of gene expression. Planaria exhibit unparalleled powers of regenera-

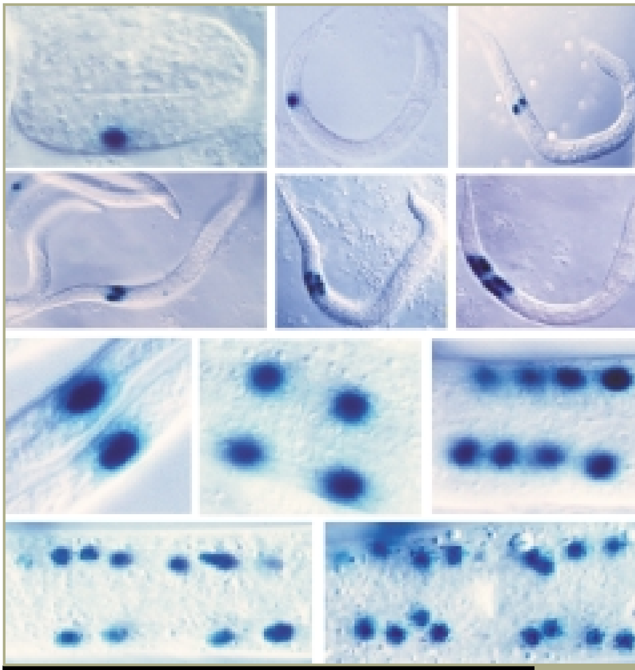

Fig. 2. This image shows the use of transgenic technology to track a single cell lineage during development. In these animals, *C. elegans*, production of a reporter protein (indicated by the blue color) is driven by control signals from the *hlh-8* gene (normally expressed in a specific mesodermal cell lineage, the M lineage). Members of the Fire lab use animals from this transgenic line to accurately assess the fate of cells derived from the M lineage.

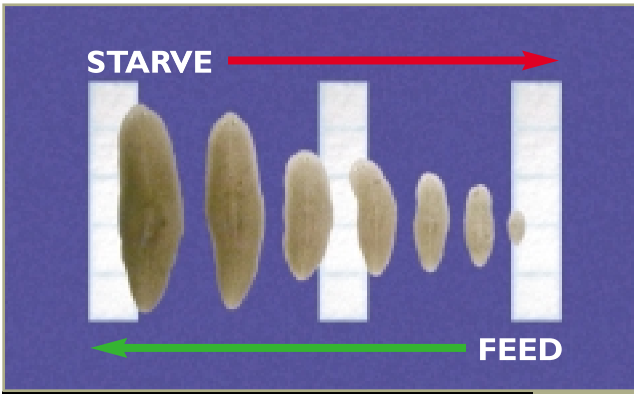

Fig. 3. Alejandro Sánchez and Phil Newmark study the flatworm *Schmidtea mediterranea*. This series shows what happens to the worm under feeding and starving conditions. With continuous feeding the planarian will grow and may reach a length of up to 20 mm. Without food it will "degrow," eventually attaining a length of less than 0.5 mm. Remarkably, this degrowth does not affect form or biological functions, which shows the existence of an exquisite homeostatic control of cell proliferation and cell death. Identifying and characterizing the molecular components regulating this function may help us understand how differentiation of tissues is attained, maintained, and regenerated.

tion that have attracted scientific interest for more than 100 years. Sánchez and Newmark discovered that planarian genes can be inactivated using RNAi and have used their new tools to identify candidate genes that seem to be important for regeneration. Their work, along with other ongoing projects in the department, continues the Carnegie Institution's long tradition of genomic studies and expands it to encompass an ever broader collection of organisms and phenomena.

News of the Department

Our seminar program was highlighted by the 23rd annual minisymposium entitled "Meiosis." Anne Villeneuve (Stanford University), Kim McKim (Waksman Institute, Rutgers University), Michael Lichten (National Institutes of Health), Patricia Hunt (Case Western Reserve University), Kelly Dawe (University of Georgia), and Barry Ganetzky (University of Wisconsin) each presented one-hour talks.

Support of research in the department comes from a wide variety of sources. Doug Koshland, Yixian Zheng and I, and various members of our laboratories are employees of the Howard Hughes Medical Institute. Others are grateful recipients of individual grants from the National Institutes of Health, the John Merck Fund, the G. Harold and Leila Y. Mathers Charitable Foundation, the American Cancer Society, the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation, the Pew Scholars Program, the National Science Foundation, and the Helen Hay Whitney Foundation. We remain indebted to the Lucille P. Markey Charitable Trust for its support.

—Allan Spradling

Members of the Department of Embryology, November 2000. First row (from left): Yixian Zheng, Phil Newmark, Bill Kupiec, Bob Levis, Allen Strause, Alexi Tulin, Dianne Stewart, Olivia Doyle, Mark Milutinovich, Chen-Ming Fan, Andy Fire, Hoi Yeung Li, Steve Tsang, Ming-Ying Tsai, Ben Remo, Alejandro Sánchez Alvarado, Heather Henry, Sasha Tsvetkov, Tom McDonaugh. Second row: Allan Spradling, Horacio Frydman, Andy Wilde, Alex Schreiber, Josh Gamse, Mike Sepanski, Don Brown, Terence Murphy, Jim Wilhelm. Third row: Kan Cao, Allison Pinder, Lijun Zhang, Erika Matunis, Marnie Halpern, Rachel Cox, Toshi Kai, Hongjuan Gao, Alice Chen, Ru Gunawardane, Glenese Johnson. Fourth row: Pat Cammon, Ellen Cammon, Ona Martin, Chris Murphy, Christine Norman, Ella Jackson, Sofia Robb, Jennifer Prowell, Jie Deng, Eileen Hogan, Hui Jin, Chiyoko Kobayashi, Daniela Drummond-Barbosa, Audrey Huang, Bruce Hodess, Rejeanne Juste, Nicole Mozden, Craig Garafola, Sofia Lizarraga, Lisa Timmons, Judith Yanowitz, Kelly Liu, Jamie Fleenor, Chris Wiese, Liquan Cai. Fifth row: Hong-Guo Yu, Zheng'an Wu, Melissa Pepling, Joe Gall, Tim Mical, Amy Hennessey, Sandra Kneissel, Shin-ichi Kawaguchi, Michelle Macurak, Biswajit Das, Rachel Brewster, Eleni Goshu, Ronald Roane, Tavon Burton.

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July 1, 1999 – June 30, 2000

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[1] From May 22, 2000
[2] To July 31, 1999
[3] To December 31, 1999
[4] To February 29, 2000
[5] To April 6, 2000
[6] From October 18, 1999
[7] To December 7, 1999
[8] From August 2, 1999
[9] To June 30, 2000
[10] From September 1, 1999
[11] From June 26, 2000
[12] From December 6, 1999
[13] From June 15, 2000
[14] To May 1, 2000
[15] From March 27, 2000
[16] To March 31, 2000
[17] From January 30, 2000
[18] From May 1, 2000

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