and job stress are the only behavioral risk factors that are worse for men.

Constance Nathanson of the Johns Hopkins School of Public Health pointed out that the longevity gap is more pronounced among blue-collar people than among the college-educated, presumably because blue collar men have worse health habits, such as smoking. "The gap is as much a product of social class as of gender," she said.

Some biology-related behavioral data were offered at the meeting, but there were no findings bearing directly on the gender gap. Ronald Glaser and Janice Kiecolt-Glaser of Ohio State University reported on studies with medical students and nursing home residents demonstrating that routine stress can affect certain aspects of immune response. But no sex differences were reported.

Martin E. P. Seligman of the University of Pennsylvania, who has done research on "learned helplessness" and depression in rodents, reported that his studies on "explanatory style" indicate that optimists probably are healthier and longer-lived than pessimists. He linked attitudes with immune response through a study of human subjects assaulted with "inescapable noise." After exposing subjects to a yeast antigen that produces a red spot on the skin, he found that the uncontrollable noise reduced the immune response of the optimists but had no effect on the pessimists, "who'd given up anyway." However, he did not see any ready relevance to sex differences, citing individual differences instead.

The conference was a worthy attempt at bringing an interdisciplinary focus to bear on the gender gap, but it became clear that this area of investigation is still quite new. As Verbrugge said, "This interest is only recent because sex differences were expected and unquestioned in all areas of life, including mortality." In many cases, the research being discussed had little direct bearing on the subject at hand. "It's hard to get biologists concerned with gender differences," said NIA associate director Matilda White Riley. And behavioral scientists concerned with the relation of biology to behavior do not seem to be the same ones who are interested in gender differences.

Furthermore, it has yet to be ascertained which level of inquiry would be most fruitful for answering certain questions. For example, why is marriage better for male health and longevity, and urbanization better for women?

Interdisciplinary research may be the answer. But by the end of the conference it appeared to some participants that the time is not yet ripe for a synthesis. ■

CONSTANCE HOLDEN

Oncogene Linked to Fruit-Fly Development

The Drosophila *counterpart of* int-*1, an oncogene originally identified in mouse mammary tumors, is the developmental control gene* wingless

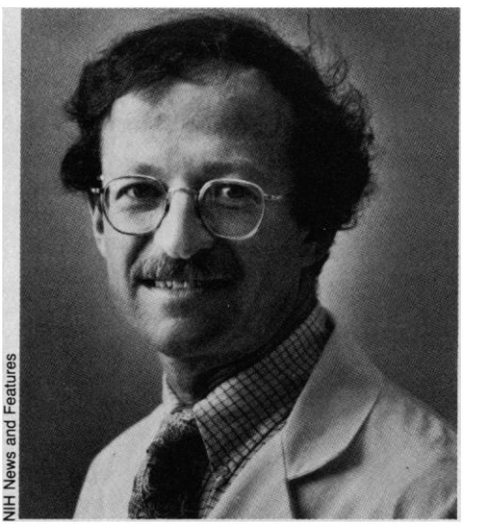
THE leap from mouse mammary tumors to fruit-fly embryos is not as big as it might appear. Within the past few months, researchers have found that *int*-1, an oncogene first identified in the mouse tumors has a closely related counterpart in the fruit fly—namely, *wingless*, a developmental control gene that was named for the first mutant identified, which lacked normal wings.

"It is the first time an oncogene has been found to be so highly homologous, and we think functionally identical, to a *Drosophila* developmental gene," says Roel Nusse of the Netherlands Cancer Institute in Amsterdam. The work provides further support for the idea that oncogenes, which can cause cells to become cancerous, are normal growth or differentiation genes that have malfunctioned in some way.

Moreover, the *int*-1 product may be a "morphogen," at least in the fruit fly, and perhaps in mammals as well. Although developmental biologists have long postulated the existence of morphogens, substances that are supposed to elicit developmental changes by virtue of their patterns of distribution in the embryo, identification of the agents has proved difficult. The developmental consequences of *int*-1 activity apparently differ in mouse and *Drosophila* embryos, however.

Until about 6 months ago, the work on *int*-1 and *wingless* proceeded on two independent fronts. Nusse originally identified the oncogene about 5 years ago while working with Harold Varmus at the University of California, San Francisco. The investigators were studying the action of mouse mammary tumor virus (MMTV), which causes cancerous tumors even though it does not carry an oncogene the way many other animal cancer viruses do. Nusse and Varmus hypothesized that MMTV acts by inserting its DNA into the mouse genome and activating the oncogenic potential of an endogenous gene.

They went on to show that about two-thirds of the mammary tumors from a mouse strain that is highly susceptible to



NIH News and Features

Harold Varmus *and Roel Nusse identified the* int-*1 gene in tumors caused by the mouse mammary tumor virus.*

MMTV have viral DNA inserted at the same site—near the gene that they called *int*-1 (for integration site–1). "It was the first gene to be implicated as an oncogene only on insertional grounds," Varmus says.

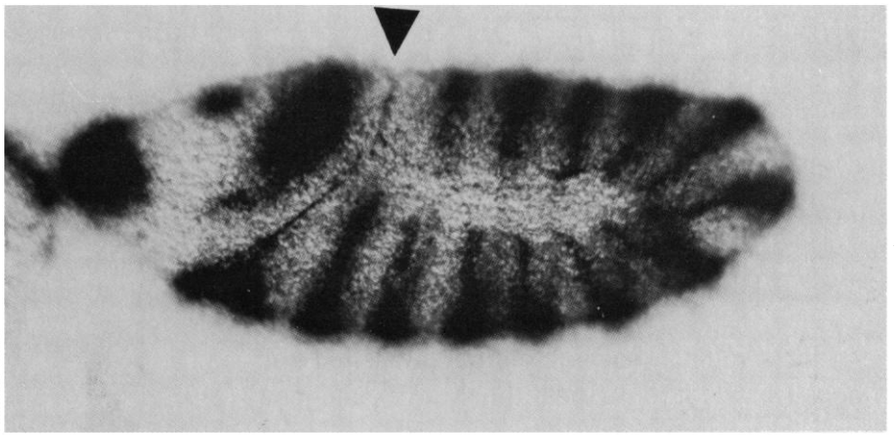
The mouse *int*-1 gene was subsequently cloned and sequenced by Nusse and Albert van Ooyen of the Netherlands Cancer Institute and also by the Varmus group. Nusse and his colleagues have now isolated the *Drosophila* counterpart of *int*-1 by using the mouse gene as a probe.

The two genes have turned out to be very similar, despite the wide evolutionary separation between fruit flies and mice. Nearly 55% of the 370 amino acids of the mouse gene also occur in the *Drosophila* gene sequence, and another 13% are of the same structural type in the two genes. However, the *Drosophila int*-1 protein is 98 amino acids longer than the mouse protein, largely because the *Drosophila* gene contains an insert encoding an extra 85 amino acids that are not present in the mouse *int*-1 protein.

According to Nusse, the discovery that the *Drosophila int*-1 gene is located at the same chromosomal site as *wingless* was the

first indication that the two genes might be identical. At about the same time that the Amsterdam workers were cloning *int*-1, Nicholas Baker, who was then working with Peter Lawrence at the Molecular Research Council Laboratory of Molecular Biology in Cambridge, England, was cloning *wingless* and mapping its chromosomal location.

On learning that the *Drosophila int*-1 gene might be *wingless*, Lawrence and his colleagues determined enough of the nucleotide sequence of their gene to establish its identity with *int*-1. "You have these two pieces of work coming from two different groups, and within 1 month it turns out we are doing the same thing," Lawrence notes. The Cambridge group has also shown that they can duplicate the developmental abnormalities of *wingless* mutants by injecting normal *Drosophila* embryos with an antisense messenger RNA that prevents the synthesis of the *wingless* protein.



Nicholas Baker

***Wingless* expression in the *Drosophila* embryo.** *At the stage of development at which this micrograph was made, the* Drosophila *embryo is folded over so that the posterior end (arrowhead) is pushed up against the head (to the left of the arrowhead). The* wingless *gene is expressed (dark stripes) in 14 segments, beginning to the right of the arrowhead and counting around the embryo to the cephalic furrow that divides the head from the rest of the body. The head shows additional areas of expression.*

The *wingless* gene has much more extensive effects on fruit-fly development than its name indicates. The original mutation, which produced the relatively modest change of replacing the true adult wing with another structure called the notum, did not completely abolish the activity of *wingless*. Mutations that destroy the activity of the gene cause major disruptions in the development of the embryonic body segments and kill affected embryos before they hatch.

The *int*-1 gene may also be involved in regulating development in mouse embryos. Varmus and his San Francisco colleagues Gregory Shackleford, Aya Jakobovits, and Gail Martin have shown that the gene is expressed in the embryonic nervous system during roughly the middle third of the 21-day gestation period of the mouse. Andrew McMahon and his colleagues at the National Institute for Medical Research in Mill Hill near London have made similar findings and defined more specifically the neural cells expressing the *int*-1 gene. The only adult cells of the mouse in which *int*-1 is normally expressed are the immature sperm cells, according to Shackleford and Varmus.

Comparing *int*-1 expression in the mouse to that in *Drosophila* does not provide any clues to the role of the gene in development. "The big problem," Baker points out, "is that the pattern of expression of *int*-1 in the mouse is unrelated to that in *Drosophila*." Nevertheless, the high degree of conservation of the protein structure during evolution suggests that it works in a similar fashion at the cellular level in the two species, even if the overall results are different.

The current best bet is that the *int*-1 protein conveys information from cell to cell. In *Drosophila*, the activity of the protein is apparently not limited to the cells producing it. For example, Baker, who is currently at the University of California, Berkeley, has found that the *wingless* gene is active in a narrow strip of cells near the rear border of each embryonic segment, but the effects of mutations in the gene extend beyond this region. This suggests that the cells that synthesize the *wingless* protein secrete it, thereby allowing it to move to cells located some distance away.

The same may be true in mouse cells. Varmus and Anthony Brown of UCSF have shown that expression of *int*-1 in cultured mammary epithelial cells causes them to take on certain characteristics of cancer cells. This does not happen with cultured mouse fibroblasts; the transforming effects of the gene are apparently limited to the mammary cells. However, when normal mammary epithelial cells are grown with fibroblasts that are making the *int*-1 protein, the mammary cells acquire the cancerous properties, a result indicating that the change may be caused by secretion of the *int*-1 protein by the fibroblasts.

Mammary cells making the *int*-1 protein, Varmus notes, do not produce tumors when injected into mice. Additional changes are apparently required to complete the cancerous conversion of the cells, a possibility in keeping with current views about the multistep nature of cancer development.

The structure of the *int*-1 protein is consistent with the hypothesis that it is secreted. "The structure of *wingless* predicts that it is secreted and may act on surrounding cells," Nusse says. The protein has a "signal sequence," similar to those carried by proteins known to be secreted, that could direct it into the pathway that would carry it to the cell exterior. Moreover, Varmus and Brown have shown that it enters the secretory pathway, although for largely technical reasons they have not yet been able to show that it is transported out of the cell. "All the indications are that *int*-1 makes a protein that is secreted and acts as an intercellular morphogen." Varmus says. "But a lot of information is required to sustain that view."

A high priority for all the investigators is the production of specific antibodies that would allow them to trace the location of the *int*-1 protein. Such antibodies would help to determine whether the protein is secreted and behaves as postulated, but so far have been hard to produce, possibly because the protein's structure has been so well conserved during evolution.

Experiments to study the function of *int*-1, especially whether the *Drosophila* and mouse proteins can replace one another, are also planned or in progress. Gene transfer methods will readily allow the introduction of the mouse gene into *wingless* mutant *Drosophila* embryos, and the fruit-fly gene can be introduced into cultured mouse mammary cells, or even into living mice.

The *int*-1 oncogene had not previously attracted a great deal of research interest, but that situation now seems likely to change. As Lawrence notes, "If we can understand a gene in any organism, it will be *Drosophila*." ■ JEAN L. MARX

ADDITIONAL READING

N. E. Baker, "Molecular cloning of sequences from *wingless*, a segment polarity gene in *Drosophila*: The spatial distribution of a transcript in embryos," *EMBO J.* **6**, 1765 (1987).

C. V. Carbrera *et al.*, "Phenocopies induced with antisense RNA identify the *wingless* gene," *Cell* **50**, 659 (1987).

F. Rijsewijk *et al.*, "The *Drosophila* homolog of the mouse mammary oncogene *int*-1 is identical to the segment polarity gene *wingless*," *ibid.*, p. 649.