heat and ozone from the tropical stratosphere, where abundant sunlight makes for high ozone production, toward the pole. Ronald Nagatani and Alvin Miller of NOAA's Climate Analysis Center in Camp Springs, Maryland, have compared a measure of the forces driving those winds in September with October temperatures and ozone concentrations at 70°S, near the edge of the chemically perturbed region. All three properties varied together between 1979 and 1985, the correlation coefficient for forcing and ozone being a high 0.91. The overall trend was downward as the amount of ozone left in the springtime hole decreased. The same relation held in 1986, when the hole's depletion was less than in 1985. The driving forces this past September were between those of the two previous years, Miller reports, suggesting that the hole would be deeper this year than last. As of mid-September, ozone within the hole had fallen to levels 15% lower than it had in 1985, heretofore the deepest hole seen. The final extent of the 1987 thinning will not be known until early or mid-October.

What all this means for the world outside the springtime Antarctic may be a bit clearer than it was before. Watson at first declined to speculate, but he eventually conceded that "I could speculate that it has been a change in both meteorology and chemistry." The future course of the climate change would be anybody's guess. Whether ozone and heat transport toward the South Pole will slow further, lowering springtime ozone outside the hole even more and freezing out more ice particles within the hole with their attendant ozone destruction, cannot be predicted.

As to the rest of the globe, "If this picture holds up—the mechanism of ice particle formation and surface reactions—then the question would be how frequently similar conditions occur elsewhere. We believe the required conditions are unique to the Antarctic. They are probably not extensive elsewhere." Stratospheric aerosols outside polar latitudes are far less abundant and consist of liquid sulfuric acid droplets, not frozen water. Their surfaces might not accelerate reactions involving chlorine. If freezing out of nitric acid is crucial to releasing large amounts of active chlorine, accelerated ozone destruction might not occur outside the Antarctic and parts of the Arctic, Watson noted.

Watson sees no reason at this point to reconsider the planned international reductions of chlorofluorocarbon production agreed to last month in Montreal. A review of the scientific basis for the Montreal Protocol is already scheduled for 1989. ■

RICHARD A. KERR

Why Do Women Live Longer Than Men?

Mortality is higher among males from conception to old age; but females suffer more from nonfatal illness and autoimmune disorders

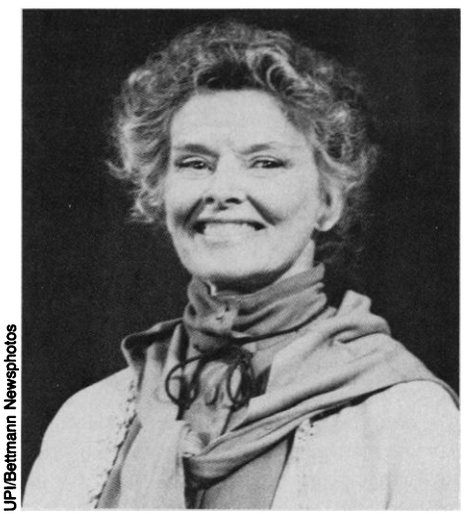
WOMEN outlive men by a margin of 4 to 10 years throughout the industrialized world. The reasons are both behavioral and biological—in the first half of the life-span, masculine tendencies to violence, as measured in homicides, suicides, and accidents, take an excess toll. In the latter half, cardiovascular disease accounts for most of the gap.

The gender gap was the subject of a recent conference called by the National Institute on Aging (NIA), which attempted to integrate some of the findings from biology and behavior. Although epidemiological studies have provided a wealth of information on relative morbidity and mortality between the sexes, the causes of the differences are poorly understood. Yet unraveling this question would yield important information both on sex differences and on the causes of longevity.

Now that females are no longer being felled by childbirth, it has become clear that they enjoy an advantage in both psychological and biological robustness. Said James V. Neel of the University of Washington, "we really are the weaker sex, biologically less fit than females at every step of the way."

The differential starts at conception. The ratio of males to females conceived is believed to be about 115 to 100; yet this advantage is pared to about 105 by birth owing to the male excess in spontaneous abortions, miscarriages, and stillbirths. "In utero it's a jungle—prime time for natural selection," said Neel. Males also have a higher neonatal and infant death rate. The male preponderance continues to erode in adolescence and by age 30, the sex ratio is equal. By 65, said Kenneth Manton of Duke University, 84% of females and 70% of males are still alive.

According to Deborah Wingard of the University of California, San Diego, who reported on a longitudinal study of 5000 adults in Alameda County, the male-to-female death ratio is the highest for homicide, at 3.9 to 1, followed by lung cancer, suicide, pulmonary disease, accidents, cirrhosis, and heart disease (2 to 1).



UPI/Bettmann Newsphotos

Katherine Hepburn: *Golden years.*

The good news is that the gender gap has not gotten any worse in the past 4 years—primarily because of men's changing habits with regard to smoking, exercise, and cholesterol consumption, which has resulted in a significant drop in the death rate from heart disease.

Nonetheless, maleness seems to carry intrinsic risk. This was illustrated in a provocative if puzzling investigation carried out by Kirby Smith of Johns Hopkins University, who has been studying the little-understood Y chromosome. Smith has been looking at death rates in four generations of an Amish family. The males in this family are functionally normal but karyotyping has revealed that they are missing the long arm of their Y chromosomes. Smith compared the average life-spans of males and females with those of two nearby Amish families. He found that among the comparison families the women lived to their mid-70s and the men died 5 or 6 years earlier. In the family with the deletion in the arm of the Y, the women lived on average to age 77.4, while the 14 men substantially outlived them, to an average age of 82.3. Smith does not know what genes might have been in the missing arm—so far there is only one identified Y gene, a cell-surface antigen. Perhaps, he said, this

study demonstrated that "too much Y and you die."

Findings at the genetic level do not always imply a female advantage. For example, Stanley M. Gartler of the University of Washington reported on differential X inactivation in the female. Females are born with two X chromosomes but obviously have to operate on the instructions of only one set of genes. Thus, one X gets inactivated early in development. Both X's have to be activated for the production of germline cells, but then one is again inactivated. With this switching on and off, there is potential for error that does not exist in males, who have only one X. All this might be expected to lead to an increase in mortality and lowering of longevity for females, said Gartler.

However, Gartler and other speakers believe that this liability is more than offset by the "mosaic nature of the female." This refers to the fact that women have two sets of X-linked genes from which to choose, and different cells can operate on instructions from genes on different X chromosomes. That is why males more often suffer from X-linked defects, such as muscular dystrophy, which are usually recessive genes. If a female is heterozygous for the disease she can operate on the good gene, whereas if a man has an X-linked gene for muscular dystrophy he will get it, since that is the only X he has.

This mosaicism might also suggest a link between female longevity and the X linkage of DNA polymerase alpha, which is the principal enzyme in animal cells for DNA replication and repair. Mutation of one of these genes might favor female survival. Yet David Korn of Stanford Medical School, who discovered the X linkage, said that at this point "I have no idea how this might or might not affect the gender gap."

The hormonal situation also seems to put males at a disadvantage biologically if not behaviorally (the possible effects of hormones on behavior were not discussed). Males and females have equivalent cholesterol levels until puberty. Males suffer an exponential increase in heart disease in their 40s, but the female rise does not start until a decade later, after menopause. There seems to be no question, from animal and human studies, that estrogen protects against heart disease by lowering levels of low-density lipoproteins (LDL), the bad cholesterol, and keeping high-density lipoproteins (HDL), the good cholesterol, up. Androgen, conversely, lowers HDL and raises LDL.

Alfred D. Steinberg of the National Institute of Arthritis and Musculoskeletal and Skin Diseases suggested that scientists could broaden the scope of studies of direct and indirect effects of androgen. For example, he has made the informal observation that football players with early male-pattern baldness do not live as long as band members.

According to William Hazzard of Bowman Gray Medical College, when androgenic anabolic steroids are given to postmenopausal women for osteoporosis, the levels of HDL are decreased and those of LDL are increased. Hazzard also said there are concerns that muscle-building steroids put athletes at greater risk for heart attacks, but there is no systematic research on the subject.

Hormones also affect the immune system. The most striking evidence of a sex differential in immune function is the fact that women are more vulnerable than men to autoimmune diseases. Arthritis plagues far more women than men (the ratio for rheumatoid arthritis is 3 to 1), as does lupus (with a sex ratio of 10 to 1) and myasthenia gravis. Marc Weksler of Cornell University related that as people age, their antibody production goes down and their autoantibodies go up. The immune system "tends more and more to become blinded to foreign antigens and more concerned with autologous antigens," particularly with women.

There is evidence from both animal and human studies that females have quantitatively greater immune responses than males. Weksler said that in one mouse study, a higher percentage of females—55% as opposed to 28% of males—rejected foreign skin grafts, and did it faster. Steinberg listed findings suggesting greater immune activity, including more tumor resistance and higher antibody responses, in a variety of species. He said androgen treatment of female mice greatly reduces their production of anti-DNA antibodies and castration in males increases it. He also said testosterone in either sex reduces anti-red cell and anti-T-cell antibodies.

The genetic, hormonal, and immunological data may eventually illuminate why females suffer different patterns of morbidity and functional disability. Wingard offered the as yet unexplained finding that whereas lung cancer rates for men and women are equal among the heaviest smokers—using a range of 20 to 50 "pack years"—there is a gender gap favoring women at the low end of the range.

Speakers said that, in general, women are sicker than men, but their disorders are less likely to be fatal. Lois Verbrugge of the University of Michigan reported that females have more acute illnesses and nonfatal chronic conditions, including arthritis, sinusitis, colitis, soft tissue disorders, chronic constipation, and bunions. Males, on the other hand, lead in emphysema, ischemic heart disease, atherosclerosis, asthma, cerebrovascular disease, and injuries.

Verbrugge said that while the reasons men die sooner appear to be to some extent biological, it is social and psychological factors that are the "main propellors" for excess sickness and disability among females. She said that most nonbiological risk factors are greater for women than men, the primary one being women's lower labor force participation. Women also experience more emotional stress, get less exercise, and feel more vulnerable to illness. She said that smoking

UPI/Bettmann Newsphotos

Twilight years: *The empty space on the sofa is usually the man's.*

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

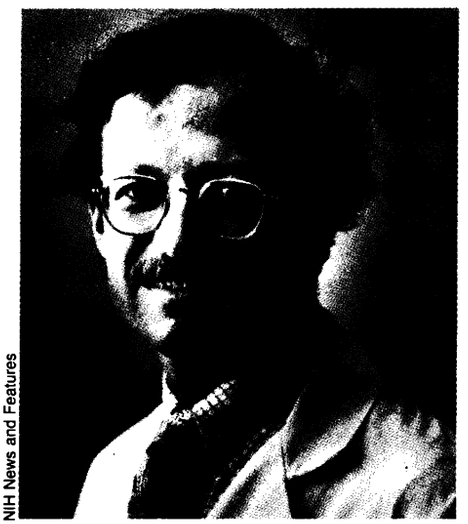
THE leap from mouse mammary tumors to fruit-fly embryos is not as big as it might appear. Within the past few months, researchers have found that *int*-1, an oncogene first identified in the mouse tumors has a closely related counterpart in the fruit fly—namely, *wingless*, a developmental control gene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