low-level exposure to an agent that is harmful at high levels (*7*, *8*).

For radiation risks, the keystone data are derived from the elegant and careful study of the survivors of the atomic bombings of Hiroshima and Nagasaki 50 years ago (*1*–*6*). In addition, cohorts of medically or occupationally exposed persons and some accidental exposures add to the database (*1*–*6*). Some 500 cancer fatalities more than would normally be expected have now been reported in the Japanese A-bomb–exposed populations (*1*). Most of these were in persons who received an acute radiation dose of more than 1 Sv (100 rem); the lowest exposed dose cohort is set at 0.2 Sv (20 rem) (*1*). Much attention has been paid to determining the lowest level for study. The comparison control group consists of all those with zero to 0.1 Sv of exposure; thus, not all received "no dose." There is another "not in city" group that also served as a parallel control population; the two control groups seem identical. The 0.2-Sv group is actually a cohort from 0.2 to 0.49 Sv, with a median of about 0.3 Sv. A discussion of whether this might be considered a threshold for effects is beyond the purpose of this discussion, especially because the uncertainties about individual radiation sensitivity, of dose, and of the possible effect of neutrons have not yet been resolved. Although a fetus is much more sensitive to radiation than an adult, the exact nature of age dependency for radiation risks is not clear, nor whether dose-rate amelioration factors are age independent.

In contrast, most people receive a normal, natural lifetime dose of background radiation of about 0.2 Sv from cosmic rays, from the radiation naturally in the Earth (including natural radon), and from the small amount of radioactivity in all tissues (*1*–*6*). We now know that continual radiation exposure is less carcinogenic than acute exposure, all else being equal (*1*). Animal studies further show that as the dose rate is decreased, the risk per unit dose not only decreases, but the latent period becomes longer (*9*, *10*). If the latent period exceeds the life expectancy, we see in the intersect the equivalent of an effective threshold (*11*). It also appears that combined exposures to both radiation and chemicals at "low" levels exert an additive and not a multiplicative effect (*6*).

It is true that fetuses and children are about twice as radiosensitive as adults, but not much more than that (*1*). It is also true that a minute fraction of the population may carry a genetic defect that renders them more radiosensitive than the norm; for example, they may lack certain genes or cellular repair tools (*6*). But even this sensitivity is less than 10 times the norm.

The evidence now available suggests that cancer induction follows more than one step (that is, it does not follow first-order kinetics), and thus a single ionization and the resultant submolecular lesion is not the whole story of carcinogenesis (*12*). The intracellular repair mechanisms of mammalian cells—the intrinsic quality-assurance systems—are designed to execute amazingly sophisticated repair and removal of such lesions (*8*). The few defects that remain may constitute the first step in the carcinogenesis process (*12*). Each subsequent step, such as altered cell division rates and supressor gene efficiency (and we do not yet know them all), has its own influence and probability of success. Risk may be the integrated sum of the failure probabilities of all the steps. Thus, the universal cancer risk curve may later prove to be more of an S or sigmoid curve. Our limited data, shortsightedly, only one order of magnitude wide, are seemingly straight-line segments of that curve.

It is time to update our thinking and policies so that a clear distinction is made between what the science says and what the policy means. The difference between the exposure levels, where almost all the data about effects lie, and the levels to which most people might conceivably be exposed is so great that it is time to seriously consider the utility of implementing a concept of an effective or practical threshold for risk, that is, negligible risk. This would be a value below that demonstrated to show harm, but not zero. It is time for us to step back and take a careful view of the way we use science to estimate possible risks from low-level exposures, especially delivered at very low dose rates. We should review the molecular biology, the newer models, the available human data, and other pertinent scientific information and decide whether to develop new paradigms for risk that better relate low levels of exposures to scientifically based determinations of potential harm.

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Notch and Wingless Signals Collide

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During development, the identities of many cells are determined by signals produced by adjacent or distant tissues. Cells often receive several signals simultaneously and must integrate them in order to take on the correct fate. Although genetic experiments can provide strong evidence for interactions among signaling pathways, whether such interactions are direct or indirect can be difficult to determine by genetics alone. In this issue, Axelrod and coworkers use both genetic and molecular techniques used to examine the interaction between the Notch (N) and wingless (Wg) signaling pathways in *Drosophila* (*1*). They show genetically that the two pathways can be mutually inhibitory and suggest that at least some of this inhibition is due to a direct physical interaction between Dishevelled (Dsh), a cytoplasmic protein required for reception of the Wg signal, and the intracellular COOH-terminus of the N protein.

Both N- and Wg-like signaling provide critical patterning information in a variety of developmental contexts and in a number of species. Our understanding of the intracellular mechanisms responsible for transducing these signals is still incomplete. N (like Glp-1, Lin-12, Xotch, and other members of the N family) is a transmembrane protein bearing extracellular epidermal growth factor–like repeats and characteristic intracellular domains (*2*). Although N can function as a receptor (*3*), it contains no previously characterized signal-transduction motifs. Rather, when bound by its ligands Delta or Serrate, N likely activates the Suppressor of Hairless [Su(H)] protein, which then moves to the nucleus and acts as a transcription factor (*4*). A recent study of mammalian homologs of N and Su(H) (mNotch and RBP-J_κ) suggests that this activation occurs by truncation of the intracellular portion of N and its

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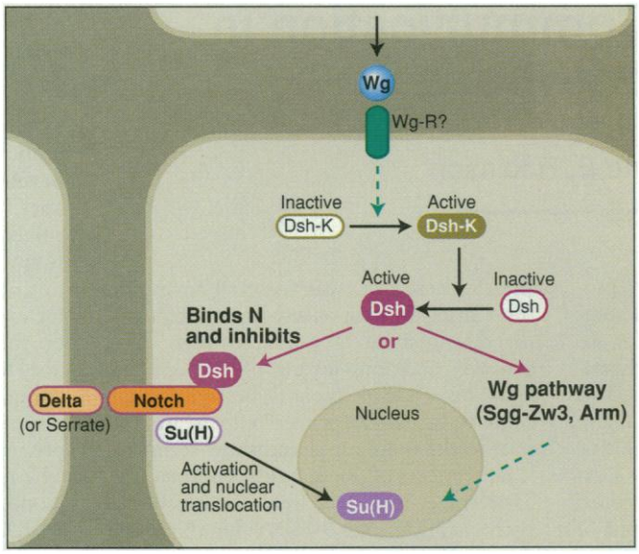
movement to the nucleus (5).

wg encodes one of several *Drosophila* members of the Wnt family of secreted growth factors, with homologs in several invertebrate and vertebrate species (6). No Wg or Wnt receptors have been identified, but the activation of the ubiquitously expressed cytoplasmic Dsh protein is thought to be a critical early step in Wg signal transduction (7). In one model, the active Dsh then inactivates Shaggy–Zeste-white 3 serine-threonine kinase (Sgg-Zw3) (the *Drosophila* homolog of GSK-3), which is also ubiquitously expressed. Sgg-Zw3 normally phosphorylates and inactivates the ß-catenin homolog Armadillo (Arm); dephosphorylated Arm is freed from the membrane and triggers Wg-dependent gene expression. These proposed direct interactions have not been proven to occur and the target of activated Arm has not been identified.



Cross talk. This hypothetical model postulates Dsh-based interactions between the N and Wg signaling pathways. Reception of Wg leads to activation of the cytoplasmic Dsh protein, which then acts through Sgg-Zw3 and Arm to affect Wg-dependent gene expression. N, when bound by its ligands Delta or Serrate, activates the Su(H) protein, which translocates to the nucleus to activate transcription. Activated Dsh may inhibit Su(H) activation by binding directly to N (*1*).

Axelrod and co-workers have examined the interactions between these two pathways during the patterning of the developing *Drosophila* wing. This appendage develops from the wing imaginal disc, an epithelial sac, with dorsal and ventral surfaces that give rise, after folding, to the dorsal and ventral epithelia of the mature wing blade. Cells within the disc epithelium are influenced heavily by cell-cell interactions in their differentiation into one of a limited number of cell types. Wg signaling is critical for the formation of wing margin bristles, and Wg is expressed in a narrow stripe of cells immediately adjacent to the bristle precursors. Wg signaling is both necessary (*7–9*) and sufficient (*10, 11*) for margin-like gene expression and bristle formation within the blade. Axelrod and coworkers show that the overexpression of Dsh induces ectopic margin bristle formation in cells distant from the Wg-expressing stripe. These bristles are still dependent on Wg and are more dense near the Wg-expressing stripe, a result that is consistent with Dsh activation by a Wg-dependent Dsh kinase (*12*).

The ectopic bristle phenotype is potentiated unexpectedly by halving the dosage of *N* in the wing, even though the density of normal bristles is unaffected by this reduction. Similar effects are apparent after reducing the dosage of the gene for the N ligand Delta; thus, ligand-bound N counteracts the effects of Dsh overexpression. The inhibition is reciprocal, because Dsh overexpression interferes with N-mediated patterning within proneural regions and during the formation of veins.

How could Dsh inhibit N function? The authors provide a potential explanation by identifying a physical interaction between Dsh and the intracellular, COOH-terminus of N and showing that it may occur in vivo: The expression of a COOH fragment of N that contains the Dsh-binding region [but lacks the site thought to interact with Su(H)] reduces the efficacy of Dsh overexpression, possibly by binding and sequestering Dsh.

Thus, Dsh binding may directly inhibit N function. If this inhibition were stronger when Dsh becomes activated, it would allow Wg to regulate N signaling. Such an interaction could regulate cell fate in the wing margin. Wg is required for the expression of proneural transcription factors in broad regions neighboring the Wg-expressing stripe. All of the proneural cells are competent to become bristle precursors, but a N-mediated competitive interaction diverts most of them into a nonbristle fate (*13*). However, the position of the bristle cells in the margin proneural regions is not random: Only those cells immediately adjacent to the Wg-expressing cells become bristles. This is exactly the expected outcome if Wg were reducing N signaling in these cells, which would then be at a competitive advantage compared with their proneural neighbors.

Inhibition of N by Dsh provides a mechanism of Wg signaling that involved Dsh, but not Sgg-Zw3 or Arm. Evidence points to the existence of such a pathway during Wg autoregulation in the embryo, in which Wg is required to maintain its own expression (*14*). However, this mechanism would also involve N in Wg autoregulation, which has not yet been established.

Hypothetically, N-Dsh binding could also explain the effects of *N* and *Delta* dosage on Dsh overexpression: Ligand-bound N could either inactivate or sequester Dsh and thus reduce the efficacy of Wg signaling. The data show, however, that expression of a N molecule lacking the Dsh-binding domain still reduces the Dsh overexpression phenotype (*1*). Thus, if N does inactivate or sequester Dsh, there are other levels at which the pathways are antagonistic.

Indeed, other levels of interaction between N and Wg pathways must exist: Many of the interactions identified genetically are synergistic rather than antagonistic (*15*). In some tissues, N is required for wg expression, which explains some of the synergism (*11–13*). However, it has also been hypothesized that Wg can itself function as a N ligand, perhaps activating an alternative signaling pathway (*15, 16*). Not all Wg-dependent events require N, so it is unlikely that N is the only Wg receptor (*13*). However, it is not yet clear whether all N phenotypes are reproduced by the loss of Su(H), so alternative N signaling pathways may exist.

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