charge exchange is easily brought about by absorbing or emitting a charged pion, so this reaction should be especially sensitive to the pion field. Again, the measurement of the spin dependence at medium momentum transfers found no change with respect to nucleon-nucleon scattering. This experiment was sensitive to the same range of pion momenta (greater than 400 MeV/c) as was probed with the antiquark distribution in nuclei.

The conclusion is that the pion field is greatly suppressed at shorter distances. As alluded to earlier, there are compelling mathematical reasons why the pion field cannot grow too large. A strong pion field at short distances leads to singularities when renormalized in field theory, contradicting the fundamental tenets of causality and analyticity (*10*). This problem is avoided in the most fundamental theory of strong interactions, quantum chromodynamics (*11*) or QCD, by introducing gluon forces as more fundamental than mesonic forces. However, the severe mathematical difficulties in making calculations in QCD leaves open the question of where the gluon field should begin to reveal itself in the internucleon forces.

Many theorists thought that the core of the nucleon was rather small, of the order of a few tenths of a fermi. But in fact the pion does not seem to show itself inside of about 1/2 fermi. From another modern point of view, this is perhaps not so surprising. Today the pion is not viewed as a fundamental particle, but as an excitation of the vacuum. The low mass is seen as a consequence of a basic symmetry of QCD, called chiral symmetry. This symmetry is respected only for very low energy phenomena, so from that point of view it is not likely to be useful inside the core of the nucleon. At short distances, the QCD degrees of freedom should become important and it is natural to ask about the role of the gluon fields.

The corrected electron scattering experiment from nuclei had shown the quarks to be depleted at higher momentum, but not enhanced at lower momentum, leaving a net depletion. There is a momentum sum rule for the quarks and gluons together, so the quark depletion requires a gluon enhancement. The gluon fields of nucleons certainly overlap at distances characteristic for the intermediate range nuclear forces. There is no reason why these should not be modified in nuclear matter or dense hadronic matter. An interesting area for future research would be to study the gluon distributions more closely.

Another idea that has been advanced is that masses of the mesons might change in the environment of the nucleus, due to quark and gluon effects (*12*). This could alter the balance of forces, reducing the influence of the pion field. The mass shifts might give measurable effects in the production of electron pairs in nuclear collisions, and this will be a subject of future study at heavy ion accelerators.

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Genetic Models for Studying Cancer Susceptibility

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It is becoming well recognized that the development of cancer is not simply a result of random events and environmental hazards but can depend on an individual's genetic composition as well. Approximately 10% of individuals who develop melanomas, for example, carry an inborn susceptibility for that cancer. Identification of the specific genes involved has obvious implications both for detection of susceptible individuals and for the development of new treatments. Recent well-organized efforts by many groups have begun to identify several candidate melanoma susceptibility loci on the short arms of chromosomes 1 and 9. Unfortunately, as one might predict, melanoma formation involves a complex web of interacting factors whose overall design remains obscure.

Two fish of the genus *Xiphophorus*, the platyfish (*X. maculatus*) and the swordtail (*X. helleri*)—both indigenous to the jungle streams of Central America—provide an extensive genetic model for identifying melanoma susceptibility genes. These fish have a grey-silver color that is due to a uniform patchwork of small black pigment cells (micromelanophores). These cells originate as melanoblasts and differentiate through a melanocyte stage as do their human counterparts. Some platyfish have much larger clusters of pigment cells (macromelanophores) that result in visible spots. It has been known since the 1920s that when spotted platyfish mate with nonspotted swordtails, some of their progeny will develop benign melanomas and some will develop malignant melanomas.

Forty years ago Breider hypothesized that melanoma formation in *Xiphophorus* resulted from the loss of "inhibitory" genes that suppressed species-specific macromelanophore genes (*1*). This proposal represents one of the first references to the concept of interacting tumor suppressor genes and oncogenes. In an elaboration of the idea, Anders (*2*) showed that the dominant tumor formation gene (*Tu*) present in the platyfish is under the control of a repressor gene (*R*). The malignant melanomas only form in the hybrid crosses of the F_1 with the *X. helleri* if the *R* gene is absent (see figure).

Three years ago Schartl and his co-workers cloned the gene at the *Tu* locus by a reverse genetics approach—that is, by determining chromosome location, finding nearby genetic markers, and isolating the correct candidate gene (*3*). The gene encodes a membrane receptor tyrosine kinase, called "Xmrk" (for *Xiphophorus* melanoma receptor kinase), that is similar but not identical to the *Xiphophorus* epidermal growth factor receptor. All *Xiphophorus* express a 5.8-kb *Xmrk* proto-oncogene transcript. A separate 4.7-kb transcript is only expressed in the melanomas of the fish with the *Tu* gene. This 4.7-kb transcript is expressed at low levels in benign melanomas and at high levels in malignant melanomas. An essential missing piece in the puzzle has been an understanding of how *R* controls the *Xmrk* gene.

Important clues to the origin of the interaction between the *R* and *Xmrk* genes have come from comparative sequence analysis of the oncogenic and proto-oncogenic forms of *Xmrk*, reported by Adam and his co-workers in this issue of *Science* (*4*). The transcripts from the two genes differ in length by 1 kb but show colinearity downstream of codon 10. The GC-rich sequences present in the 5' end of the *Xmrk* oncogene are missing from the oncogene and are replaced by TATA- and CAAT-like sequences from another gene. Using reporter gene constructs, Adams

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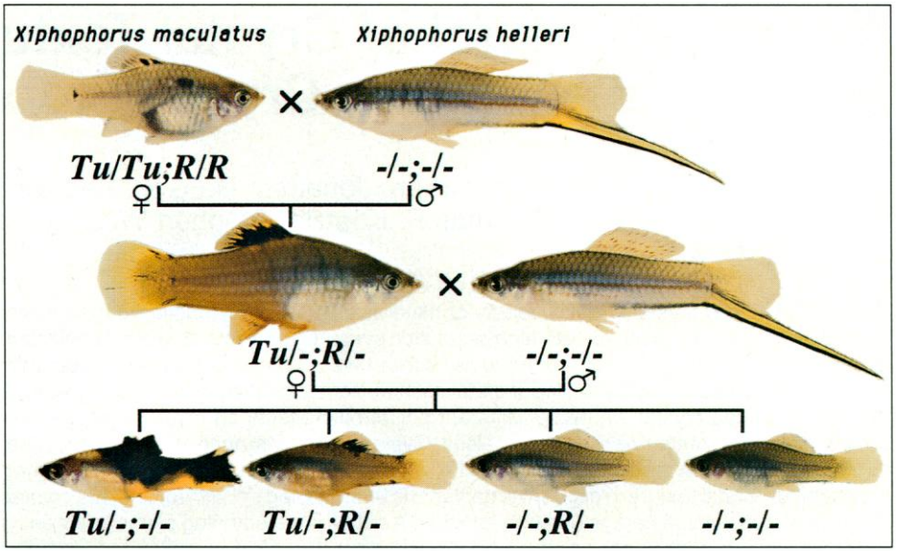
and co-workers showed that the 5' fragment from the oncogenic form of *Xmrk* is a strong promoter in melanoma cells that do not carry the *R* locus. Mapping experiments revealed that this 5' fragment is present not only in the *Tu* locus but also in a separate locus (*D*) found in all *Xiphophorus*. These results suggest that the *Tu* locus arose by nonhomologous recombination of the *Xmrk* proto-oncogene and the *D* locus; such an event would generate an *Xmrk* gene that is overexpressed because it has acquired promoter sequences from the *D* locus. The recombined form of *Xmrk* is present in all *Xiphophorus* with the *Tu* locus. The control of melanomas by the *R* locus can thus be viewed as "an accidental side effect of the regulation *R* exerts on *D*" (4).

Although the presence of *R* may be considered accidental, it is essential to the survival of fish carrying *Tu*. It is within this byzantine context that the *Xiphophorus* model offers an example of how one can inherit an activated dominant oncogene, yet, because of the coincident presence of its repressor, only develop isolated clonal melanomas. So far there are no human cancer susceptibilities attributed to the inheritance of activated proto-oncogenes.

When the first human tumor suppressor gene was cloned (5), there was a tendency to highlight differences between growth-limiting genes and the better understood dominant oncogenes. This led some workers to use dramatic labels such as "anti-oncogenes," which were reminiscent of the separate worlds of matter and anti-matter. Since then, more and more examples suggest immediate and direct interactions between these two sets of genes. For example, the product of the human retinoblastoma susceptibility gene (*RB*) modulates the activity of transcription factor E2F, whose binding sites are found in the promoter sequences of many growth-activating genes such as MYC (6, 7). The product of the neurofibromatosis-1 (*NF1*) tumor suppressor gene can help shift the *ras* oncogene product to an inactive form (8). The interactions between *Tu* and *R* are yet another clear example of how important these interactions between oncogenes and tumor suppressor genes can be. As cancer susceptibility models such as *Xiphophorus* are developed, the power of genetics can be harnessed to explore more of the signaling pathways involving tumor suppressor genes. Both *Drosophila* and *Caenorhabditis elegans* have already provided information about the *ras* control pathway that rivals the data gathered from mammalian systems (9, 10). The *C. elegans* system has also begun to provide rich information about the pathway by which the *bcl-2* oncogene controls cell death (11, 12). Homologs of tumor suppressor genes have yet to be identified in *C. elegans*.



Inheritance of melanoma in *Xiphophorus*. Classical genetic cross illustrating the development of melanoma in F_2 progeny that carry the *Tu* locus but not the *R* locus. The melanomas in *Tu/-;-/-* fish are highly malignant, whereas those in *Tu/-;R/-* fish are benign. [Photo courtesy of M. Schartl]

The *Xiphophorus* genetic model also shows that genetic susceptibility to a specific cancer can be a result of complicated interactions between multiple "susceptibility genes." Detection of germline mutations in tumor suppressor genes such as *p53* and *RB* may allow identification of individuals at high risk for cancer. Nevertheless, the interactions between the *Tu* and *R* genes in *Xiphophorus* suggest that modifier genes can control cancer susceptibility genes. Although there is limited direct proof that modifier genes modulate cancer susceptibility genes in humans, there are two lines of evidence that suggest they have a role in the development of human melanomas. First, in some families linkage has been detected to genes on chromosome 1p36 (13), and in other families linkage has been detected to genes on 9p21 (14). Second, the level of penetrance varies in different families with hereditary melanomas. For example, whereas the penetrance in many families may be close to 90%, the penetrance in the 9p families is approximately 50% (15). One possible explanation for these data is that several different modifier genes are involved in the development of human melanomas. The obvious beauty of genetic systems such as *Xiphophorus* is the power to identify genes whose interactions dictate cancer susceptibility.

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