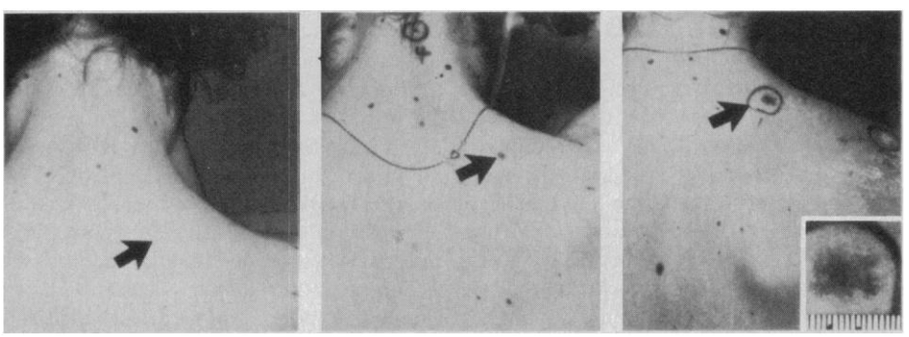
Researchers Seek Melanoma Gene

In some families, a tendency to develop unusual moles and malignant melanoma are inherited through an autosomal dominant gene

ABOUT 10 years ago, Robert Miller of the National Cancer Institute visited the American Oncologic Hospital in Philadelphia. There he heard about a family living near Trenton, New Jersey, many members of which had malignant melanoma, a deadly skin cancer. Miller returned from Philadelphia and approached Mark Greene, a newly arrived clinical associate who was looking for a research project. It might be interesting, Miller told Greene, to investigate whether members of this family inherit a tendency to develop malignant melanoma.

Thus began the NCI's melanoma project, a continuing study of the genetics of malignant melanoma that has provided evidence that members of certain families inherit a dominant gene that leads them to develop the disease. More than 90% of those who inherit the gene get melanoma. It also has led to early detection of the cancer in susceptible individuals, which enabled them to be treated while the cancer is still curable. And it has led to a search to locate the malignant melanoma gene.



The genesis of a dysplastic nevus. *Unlike ordinary moles, dysplastic nevi occur throughout life. At age 11, the girl pictured in frame (a) has a normal mole pattern. Frame (b) shows her at age 12 when she has acquired many new moles. In frame (c), she is 14 years old and a mole that was absent when she was 11 has now turned into a dysplastic nevus (inset), characterized by irregular edges and varied coloring.* [*Source:* N. Eng. J. Med. *312, 91 (1985)*]

The idea that malignant melanoma may run in families was not new at the time that Miller and Greene heard of the New Jersey family. As early as 1820, Sir William Norris wrote of a father and son who both got the disease and more recently there have been numerous reports of melanoma-prone families. But the question was, did these people share an environment that led them to develop melanoma or was their disease inherited?

Greene, who recently left the NCI to enter private oncology practice in Peoria, Arizona, began in 1976 by contacting the members of the New Jersey family, which he refers to as family K (K is the first letter of their last name). Greene asked Wallace Clark, of the University of Pennsylvania School of Medicine, "one of the world's leading melanoma pathologists" to come along to see the family. Clark agreed.

The two physicians examined the members of family K on a Sunday afternoon in April 1976. The first thing they discovered, says Greene, was that "many people in the family had unusual moles." The moles tended to be large, variably pigmented, and irregularly shaped. They also tended to be on the scalp, buttocks, and, in the women, on the breasts—all places where ordinary moles are uncommon. In addition to noticing these moles, Clark and Greene diagnosed a melanoma in a middle-aged man from family K who had come from California to be examined that afternoon. This man also had a proliferation of the odd moles.

Some of the unusual moles reminded Clark of moles he had seen on another patient earlier that year. He contacted the woman and learned that she too came from a melanoma-prone family. Other members of her family, family B, also had the unusual moles. "The project took off from there," says Greene.

Greene went to the NCI family studies computer data bank which contained information on about 3000 cancer-prone families and pulled out information on melanoma familes. Clark, Greene, and their associates ended up seeing members of 14 melanoma-prone families. They looked in particular for the unusual moles they had seen in families K and B. "Almost all the melanoma families that we studied have these funny looking moles. And virtually all the melanoma patients had these moles," says Greene.

The researchers began following these families, studying them prospectively. They learned, says Greene, that "new melanomas occurred at a dramatic rate, but only in those family members with the funny-looking moles, which we eventually designated dysplastic nevi." They also learned that most of the unusual moles do not become malignant. Because the family members frequently have hundreds of moles and because, unlike most people, they tend to develop new moles throughout their lives, it is infeasible to remove the unusual moles in an attempt to prevent the cancer from developing.

It looked at first as if these dysplastic nevi were, says Greene, "an unusual curiosity in melanoma-prone families." But it turns out that 5% to 6% of the population have one or more of these moles. "One of the big holes in our data is the estimate of risk associated with dysplastic nevi in people who are not from melanoma-prone families. It is a clinical dilemma to decide how to deal with patients from the general population with dysplastic nevi," Greene remarks. The moles may be an indication of a new mutation making these people melanoma-prone. In that case, their children could also be at high risk for melanoma. Another possibility is that the people could actually be members of poorly documented melanoma families. Or they could in fact be at low risk for melanoma.

Another unanswered question is what percentage of malignant melanoma cases arise outside of melanoma-prone families? To get an answer, says NCI geneticist Sherri Bale, "will take years of unbiased ascertainment of persons with melanoma." No one is looking yet, however. "I don't know of any

population-based studies of melanoma patients in which family histories were collected," Bale says.

However, in the well-documented melanoma families, it now appears that the presence of dysplastic nevi is the single strongest predictor of melanoma risk factor. And the melanomas that do occur arise directly from these moles. This means that the investigators can advise family members who have these moles that they are at high risk for melanoma. These people are told, says Margaret Tucker of the NCI, to avoid sun exposure and, in particular, to avoid blistering sunburns. They also are taught to carefully examine the entire surface of their skin at frequent intervals.

In the well-documented melanoma families, it now appears that the presence of dysplastic nevi is the single strongest predictor of melanoma.

The NCI investigators have so far picked up about 70 malignant melanomas in melanoma family members. "The vast majority were very early, very thin lesions that should be cured by surgery," Tucker says. There still are failures, however. Even the most vigilant surveillance cannot prevent some cancer deaths. "We had two bad failures lately," says Bale. "One was a 32-year-old woman who had never had melanoma. She developed metastatic disease with no identifiable primary tumor site and died 2 weeks ago. The other is a woman in her 30's who is pregnant and just had a diagnosis of metastatic melanoma."

In order to assess the risk to melanoma family members, NCI geneticists looked at the pattern of inheritance of dysplastic nevi and malignant melanoma. Bale reports that dysplastic nevi and the susceptibility to the cancer are inherited as though they are caused by an autosomal dominant gene with greater than 90% penetrance, meaning that those who inherit the gene have a greater than 90% chance of having the nevi and, possibly developing malignant melanoma.

If nearly everyone who inherits the gene develops the disease, it is not clear whether measures such as avoiding sun exposure will make much difference. But Greene and his colleagues find that fibroblasts and lymphocytes from members of melanoma families who have dysplastic nevi are unusually sensitive to the mutagenic effects of ultraviolet light. When cells from these persons were exposed to ultraviolet light or to chemicals that mimic the effects of ultraviolet light, they had an unusually large number of chromosomal breaks and other abnormalities. The melanoma gene, Greene and his colleagues suggest, may act by making skin cells unusually prone to mutate when they are exposed to the sun.

The next step is to look for the melanoma gene itself. Dean Mann of the NCI, Armead Johnson of Georgetown University, and Christine Murray of the Uniformed Services University of the Health Sciences, in collaboration with Bale and her associates, began by looking for an association between the HLA genes, which code for the transplantation antigens that cause rejection of grafted skin or transplanted organs, and the melanoma gene. Several researchers have reported that melanoma patients have particular HLA antigens. In addition, it is known that the HLA gene complex includes immunoregulatory genes and that melanoma occurs frequently in patients with compromised immmune systems. For these reasons, it seemed possible that the melanoma gene is very near the HLA genes and is inherited with them. However, says Bale, "we proved *conclusively* that the melanoma gene is not in the region of HLA."

Furthermore, the NCI investigators, working with David Housman and Danila Gerhard of the Massachusetts Institute of Technology, have not found evidence that the melanoma gene is near any of several oncogenes nor near several other marker genes that could help them pin down the chromosomal location of the melanoma gene.

But the work has just begun. Once they isolate the gene, researchers will be better able to address the question of whether dysplastic nevi in the general population are actually risk factors. If a person in the general population has dysplastic nevi and the melanoma gene, he probably is at high risk of getting the cancer. And, finally, it would be fascinating to know just what the melanoma gene does. How does a single gene cause cancer? And if it is not an oncogene, what is it? ■ GINA KOLATA

This is the fourth and last of a series of articles on the development of genetic tests to determine susceptibility to disease. The first three articles appeared in the 18 and 27 April and 2 May issues.

ADDITIONAL READING

M. H. Greene *et al.*, "High risk of malignant melanoma in melanoma-prone families with dysplastic nevi," *Ann. Intern. Med.* **102**, 458 (1985).

Briefing:

Venus Is Looking More Like Earth Than Mars

For a while it seemed the surface of Venus might be as fixed and immobile as that of Mercury, Mars, or the moon, those tectonically dead, alien-looking spheres that so sharply contrast with Earth and its churning plate tectonics. But Venus looks a good deal more familiar now that closer radar views, from Earth-based and Soviet Venera 15 and 16 spacecraft observations, have revealed the crumpled and torn surface typical of the jostling of segments of crust.

At the recent Lunar and Planetary Science Conference,* the Soviet Venera spacecraft team, headed by Valery Barsukov and Alexander Basilevsky of the Vernadsky Institute in Moscow, presented a summary of the geologic features mapped from the Venera imaging radars that clearly sets Venus apart from the smaller rocky planets. Horizontal motion of the venusian crust had obviously compressed it into ridges and grooves unlike anything seen even on Mars. The motion of the surface of Venus "can be compared only to that of Earth," they reported.

James Head and his colleagues at Brown University have now taken the next step in the study of venusian geology and assembled geologic features created by horizontal motion into a sequence of events. This step is controversial because it involves making sense of a surface that is tectonically more complex than the minutely photographed surface of Mars but is glimpsed imprecisely through radar. Head and his group combined radar data from the American Pioneer Venus, the Soviet Venera 15 and 16, and the Arecibo radar in Puerto Rico and discerned two episodes of crustal compression that they believe created Ishtar Terra, a continent-like highlands high in Venus's northern hemisphere.

The first episode, operating in an east-northeast direction, squeezed the crust into a series of folds in the way that a rug can bunch up on a slippery floor. That formed the predecessor of the 500,000-square-kilometer Maxwell Montes, at an altitude of up to 11 kilometers the highest area on the planet. This compression also formed a region of folded and broken crust to the east. That arrangement of folds would bear a considerable resemblance in a radar image to the Appalachians that were formed by the

*Seventeenth Lunar and Planetary Science Conference, 17–21 March 1986, Houston, Texas. Abstracts are available from the Lunar and Planetary Institute, 3303 NASA Road One, Houston, TX 77058–4399.