A Tumor in the Family

Mice, begotten in part by a rehabilitated tumor, are being used to create laboratory models of human genetic diseases

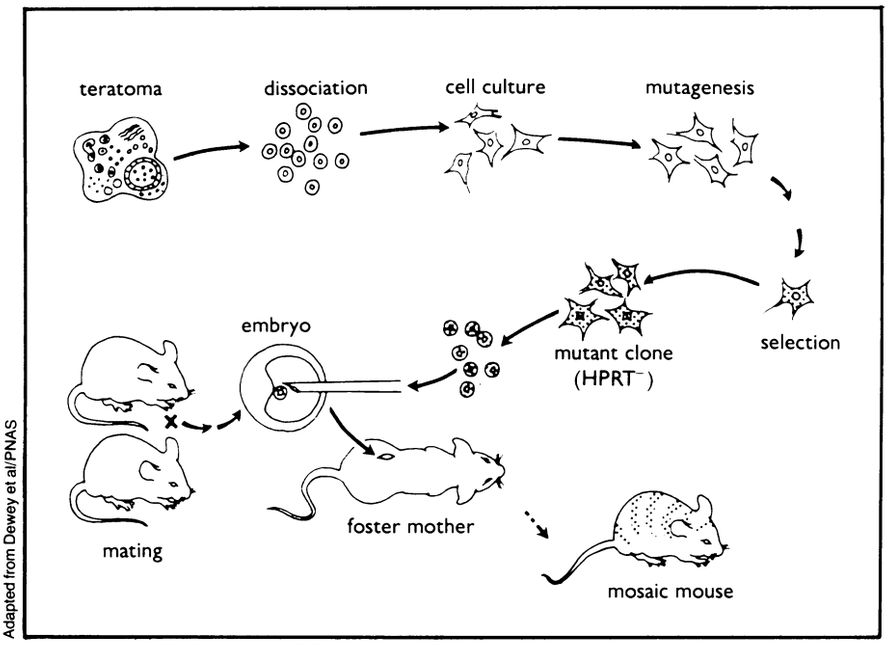
BY JULIE ANN MILLER

Turning cancer cells into mice sounds trickier than transforming common metals into gold, but the biologists have beaten the alchemists hands down. Beatrice Mintz, who was one of the originators of four-parented mice (SN: 10/22/77, p. 263), has more recently created mice with tumors in their family trees (SN: 4/16/77, p. 246). Speaking recently at the National Institutes of Health, Mintz explained that those mice have prompted new ideas in cancer theory, and went on to describe work using the tumor-bred animals to apply powerful laboratory methods, appropriate to isolated cells, to problems of development and disease in the context of the whole animal.

The tumor used by Mintz is a rare type called a teratoma, or embryonal carcinoma. Unlike most tumors, which contain cells of just one kind, teratomas are made up of a disorganized jumble of different tissues, such as bone, muscle, skin and nerves. Mintz has demonstrated that, given the proper setting, cells from such tumors can differentiate in an orderly manner into all mouse tissues. No other type of tumor is likely to be able to produce all the tissues, Mintz says, because no other tumor arises from cells so early in their development.

In Mintz's experiments at the Fox Chase Cancer Center in Philadelphia, she selects the undifferentiated, dividing "stem" cells of a teratoma and injects them into a hollow ball of normal embryonic cells (at the blastocyst stage). The cells do not fuse, but simply associate "like a collection of marbles," Mintz explains. "Each cell retains its genetic integrity." The blastocyst is then implanted into a foster-mother mouse. The investigators use coat color and also biochemical markers to indicate the contribution of host embryo and of tumor cells to the mouse that results.

A mouse containing tumor-derived tissues is no more likely to develop a tumor than is a normal mouse. "This is dramatic testimony to the influence of the tissue environment," Mintz says. "It's the first case where one can unequivocably point to a non-mutational basis for malignancy." The genes of those tumor cells remain capable of expressing themselves normally even after years of making only tumors. "The tumor hasn't forgotten its coat color even after [as a tumor] killing many mice," Mintz says.



Adapted from Dewey et al/PNAS

To create a laboratory model of human Lesch-Nyhan syndrome, biologists introduced mutations into cells derived from a tumor, selected cells deficient in the crucial enzyme and injected those cells into an embryo which then produced a mouse which is a mosaic of normal and enzyme-deficient cells.

Although for many other types of tumors there is persuasive evidence that changes in the genetic material are the source of the malignancy, Mintz's work demonstrates the existence of "non-mutation" cancers. The finding may lead to a new principle for therapy, Mintz says. "You might cure cancer by inducing differentiation of stem cells, instead of trying to kill them," she points out. Therapy thus would not wipe out tumor cells, but just leave behind the tumor characteristics.

"Mice-made-to-order" is the other aspect of teratoma-to-mouse research. Because lines of cancer cells can be maintained indefinitely under laboratory conditions, they are accessible for all the techniques of modern cell biology — such as mutation of the genes in the nucleus, introduction of foreign genes and fusion with other cells. With Mintz's technique, teratoma cells manipulated in the laboratory can later be transformed into tissue of complete mice.

One possibility now is mouse models of human genetic diseases. The researchers already have work in progress creating a mouse version of Lesch-Nyhan syndrome. That disease leads to excess formation of uric acid and to severe neurological symptoms, including self-mutilation, spasticity and mental retardation.

Mintz and Michael Dewey chemically induced mutations in teratoma cells growing in laboratory culture and then selected mutant cells unable to make the enzyme that is deficient in persons with Lesch-Nyhan syndrome. That enzyme is HPRT (hypoxanthine phosphoribosyltransferase). Teratoma cells deficient in HPRT were injected into normal embryos and many of the blastocysts developed into mice with tissues of mixed origin. The tissue sections derived from the tumor remained deficient in HPRT.

The researchers are optimistic that the "synthesis" of mice with HPRT-deficient cells will be a useful way to examine the basis of human Lesch-Nyhan disease and possibly to attempt its cure. Analysis of animals where only a few tissues contain cells derived from the tumor should be useful in determining the chief tissue

sources of the disease's symptoms. (Other mosaic animals, such as four-parented mice, can be used the same way once mutations mimicking human disease are available [SN: 11/18/78, p. 344].) Mintz and colleagues hope to propagate the genetic trait to subsequent mouse generations.

Unexpectedly, the work with mosaic mice offered insight into another disease, an anemia. Teratoma cells were found to contain a mutant gene that causes anemia. The gene is called *steel,* because of the gray banded hairs in the coats of mice with that trait.

In the mosaic mice produced from teratoma cells injected into an embryo, the blood-forming tissues with normal and with *steel* genes coexist throughout the developmental stages. Mintz and Claire Cronmiller report in the December PROCEEDINGS of the NATIONAL ACADEMY of SCIENCES that a surprisingly small number of normal cells in the blood-producing tissue's "microenvironment" can prevent the anemia from developing. However, if, in later generations, the normal cells are not present, the *steel* gene is again able to elicit the blood defect.

Mintz foresees "tremendous possibilities" for the transfer of foreign genes into teratoma cells and then into mice. Such experiments offer the possibility of learning whether genes can function in an animal under various conditions, for instance, in the absence of the genes that normally accompany them or without their flanking sequences. Eventually it may be possible to model human disease by actually moving the human gene into a mouse. Mintz anticipates "a useful arsenal to probe differentiation and malignancy."

Finally, mice derived in part from tumors offer a rare opportunity to study traits passed from mother to offspring in the cytoplasm of the egg, rather than in the chromosomes of the nucleus. Cytoplasmic organelles, such as mitochondria, carry genes; yet specific traits in mammals have not been identified. Now Mintz, working with Tomomasa Watanabe and Dewey, reports success in using mouse teratoma cells as vehicles for introducing into mice a convenient mitochondrial gene mutation, one that makes a cell resistant to the antibiotic chloramphenicol. Mintz suspects that research eventually will uncover human disease due to mutations in mitochondrial genes. The investigators say in the October PROCEEDINGS OF THE NATIONAL ACADEMY of SCIENCES, "... the precise roles of extranuclear genes in maternal inheritance and in development and diseases of mammals have remained *terra incognita* and may now become experimentally assessible *in vivo.*"

Other laboratories are beginning to pick up Mintz's technique. While having a tumor for a father is the ultimate skeleton in a mouse family closet, it may become a routine way to attack questions of development and disease in their complex context. □

... SERIES

geometry makes it ideal for geodetic purposes as well. Therefore, in order to optimize the return from this major investment of public funds, we recommend that support be provided for development and refinement of the Global Positioning System with the aim of achieving geodetic accuracy."

So it is no surprise that MacDoran is optimistic about SERIES. Similar systems also receiving support propose using communications satellites or radio sources left on the moon by astronauts, but these do not have the 3-D signal arrangement that the GPS provides. According to MacDoran, a group at Massachusetts Institute of Technology has suggested a system much like SERIES, but it would require the DOD to change its satellites. Recognizing a brick wall when he sees it, MacDoran decided to design a system that would circumvent that problem. Now, the construction and testing lie ahead.

"A lot of good people have looked at it and nobody has found any flaws," he says. "I feel good about that." □