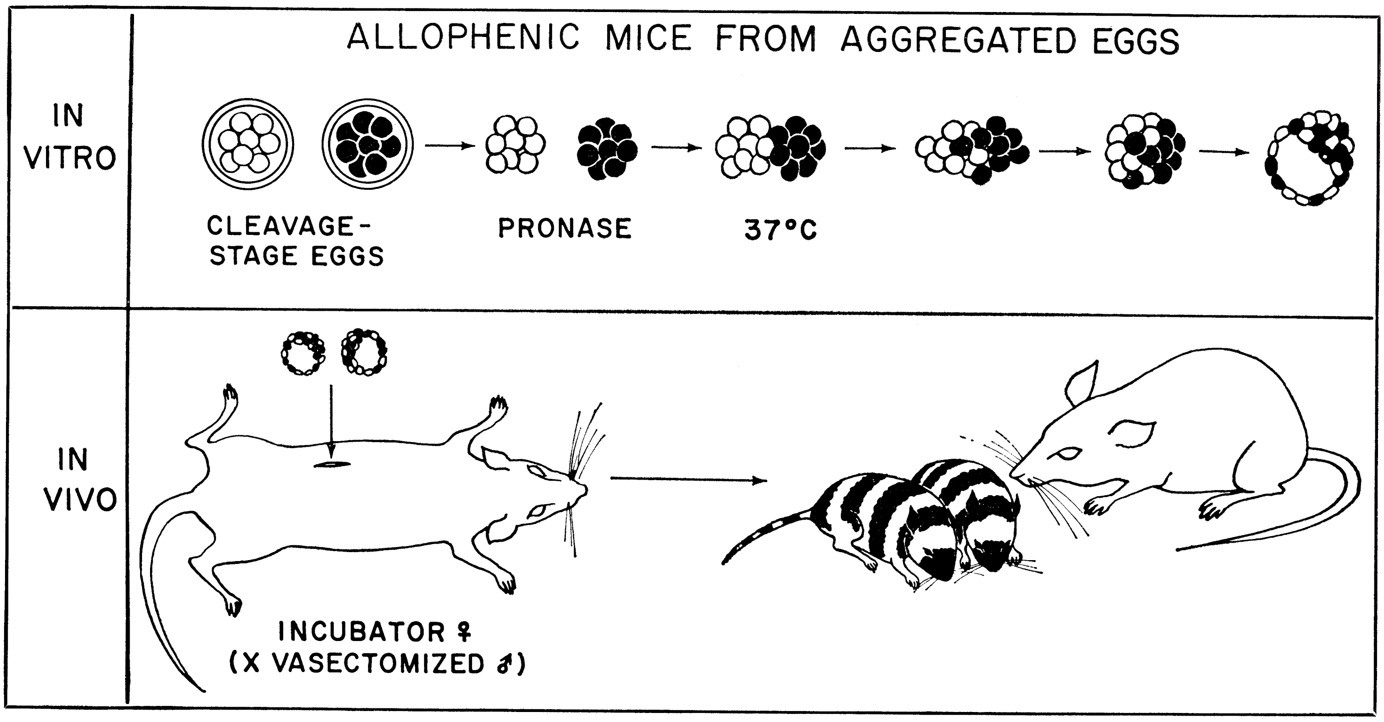
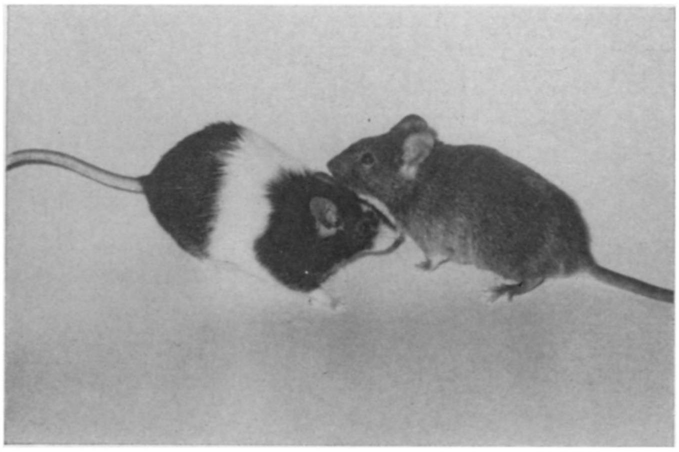


GENETICS

Two mothers, two fathers

Mice with four parents reveal secrets of heredity

by Barbara J. Culliton


Dr. Mintz

Genes from black mouse extend white's lifespan.

On New Year's Day 1965, a black and white striped mouse was born in northeast Philadelphia. It had two mothers and two fathers—the first four-parent creature in history.

Between then and now, about a thousand of these unusual animals have been created. Far from being mere laboratory freaks, they are a new tool for examination of the most basic unknowns in modern biology.

"Four-parent mice," says their maker, Dr. Beatrice Mintz, "are revealing the secrets of how heredity controls development." A developmental biologist and geneticist at the Institute for Cancer Research, she is counting on her mice to unravel the mystery of cell differentiation—the phenomenon in which cells diversify into a vast array of types even though they carry the same genetic information in a single individual.

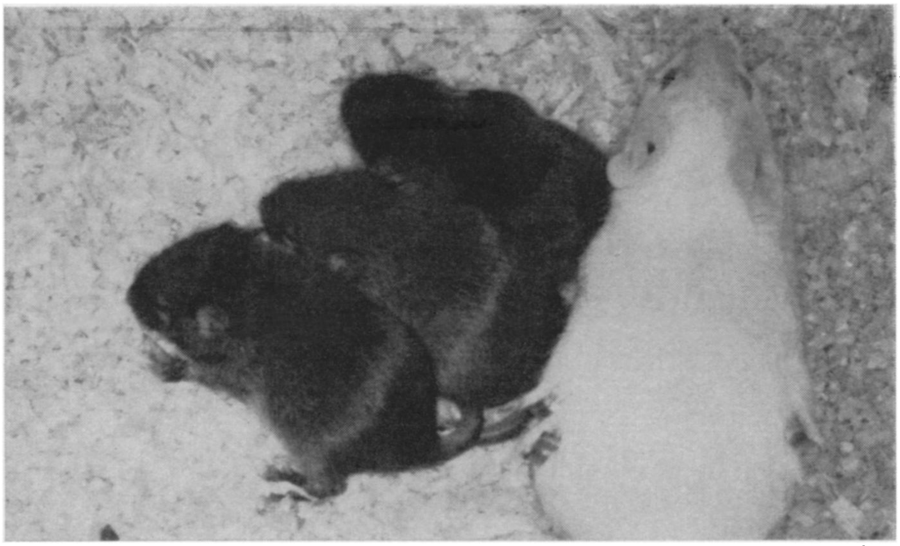
Normally, after fertilization, a single egg with a given collection of genetic information splits from one cell into two, from two to four, from four to eight, and so on until millions of cells have built a man—or a mouse. And even though one cell is blood and another heart, the genes residing in the nucleus of each are believed to be identical.

To chart the course of development, scientists need to trace the history of a blood or heart cell back to the genes that made it—a task made extremely difficult because the same genes are in all kinds of cells, even though only pieces of the total genetic package are actually being used in any one kind of cell.

Four-parent mice are beginning to show the routes, at least, to a tracer for genetic mechanisms. These genetically mosaic creatures derive genetic instructions from each set of parents; they come with two separate heredities. So their cells are tagged with different genes that are like signal flags, and Dr. Mintz is learning to decipher the developmental stories these signals tell.

In her first successful mouse-making venture, two pure black mice were mated to yield fertilized eggs and two pure white mice were mated to get another group of eggs. Then, when the embryos had barely developed, having divided into only eight cells each, Dr. Mintz removed them from the females' oviducts, put an embryo of each kind in a growth medium, and dissolved the covering membrane around each. All the cells from a black-type egg and all those from a white-type egg were then pushed firmly into one mass with a glass rod. The egg cells intermingled and the mass continued to develop as if it had always been one embryo.

Some 24 hours later, a single, com-



Dr. Mintz

This incubator mother mouse bore three four-parent babies of different colors.

Dr. Mintz

Dr. Mintz traces the genetic history of tissues from four-parent mice.

bined embryo was ready to be transplanted to the womb of a foster mother.

At first the artificially-made embryo had twice the usual number of cells and was twice normal size. But long before its birth, whatever mechanism controls size had done its job; the newborn mouse was perfectly normal in size. "That really isn't too surprising though," Dr. Mintz observes. "After all, identical twins are not half size."

The creatures were not only normal in size but were quite healthy and had all the normal parts and form of a mouse. But instead of having some chaotic mixup of black and white cells in their coats, they had regular black and white stripes on each side, going from the back around to the belly.

The two kinds of cells also had genes that could have been immunological trouble-makers. Each regarded the other as an unwelcome intruder. But the artificial mouse survived perfectly well with its two different heredities and readily accepted tissue transplanted from other animals like any of its four parents. Since the cells are in each other's company long before the immune system develops, neither views the other as foreign. Rejection of transplants from any other mice demonstrates that in four-parent creatures the immune system works.

Some of the mosaic mice have the two different genetic types of cells in all their organs, others have them in only some organs, and there are many different arrangements. For example, a mouse may have a heart with one kind of genes, a liver with another and blood with both.

With Dr. Mintz' technique of mixing embryo cells, it is possible to rig in advance the combinations of genetic information that will confront each other in the cells of an animal, and to discover from the interactions between them what the critical control systems are in a mammal.

Her thousand mice have been made in all kinds of combinations. Short-lived and long-lived strains have been combined, and health- and disease-prone strains have been combined. Many of the experiments involve strains known to have an inherited susceptibility toward cancer under certain circumstances, and mosaic mice were made with strains that naturally develop specified types of cancer, mixed with strains that normally are unlikely to get the disease.

The results yield highly precise information. In pigment studies, for example, the black and white striped animals, with 17 bands of color on each side of the spine reveal that during differentiation in the embryo, genes direct the production of 34 primordial pigment cells. From these 34, the animal derives his entire population of pigment cells; each of the 34 divides and makes exact replicas of itself.

But mixing black and white strains does not consistently result in a mosaic mouse that is striped. "The variations we get," says Dr. Mintz, "range from one end of the spectrum to the other. Some are all white, having used no black pigment cells. Some are all black. Many are a patchwork." Perfect striping appears to occur only when the two types of cells are equally successful, and there is no cell death and no unequal cell competition for space and nutrients. Frequently, some cells are more viable than others; their enzymes may be more efficient. Natural selection would favor these. Parts or all of the stripes of the other color type are then lost.

Dr. Mintz draws a parallel between selection during the evolution of species and the cell selection during development. However, she postulates, the developmental evolution of cell populations in an individual is tied to new genetic mechanisms rather than primarily to mutations. "As we learn more, I expect we'll discover a host of mechanisms of whose existence we are not now aware. And the relatively coarse distinctions we now make between cell types may turn out to be too broad; they may hide much more variability and heterogeneity than we have recognized. We'll have to learn whether there are distinctions between various kinds of red blood cells in one individual, for example, and whether there are various subpopulations in all the other kinds of cells as well."

At this stage in the course of genetic research, advances depend in part on the accumulation of new and specific pieces of information about the way genes behave. Much current knowledge is based on work with simple micro-organisms. Mosaic mice offer an opportunity to learn what is happening in a complex, living mammalian model. ◇