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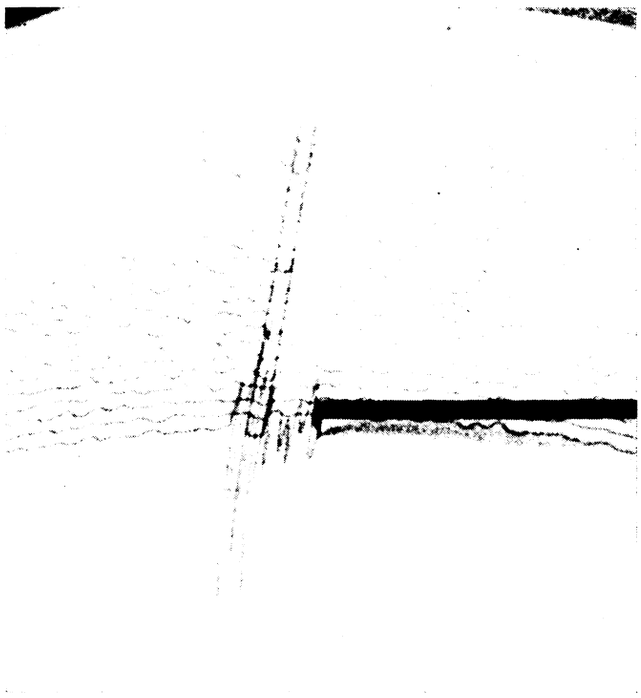


UPI

A 1968 Nevada test, Faultless, created a fissure. The Amchitka Island blast, at B, registered 6.1 on Berkeley seismograph.

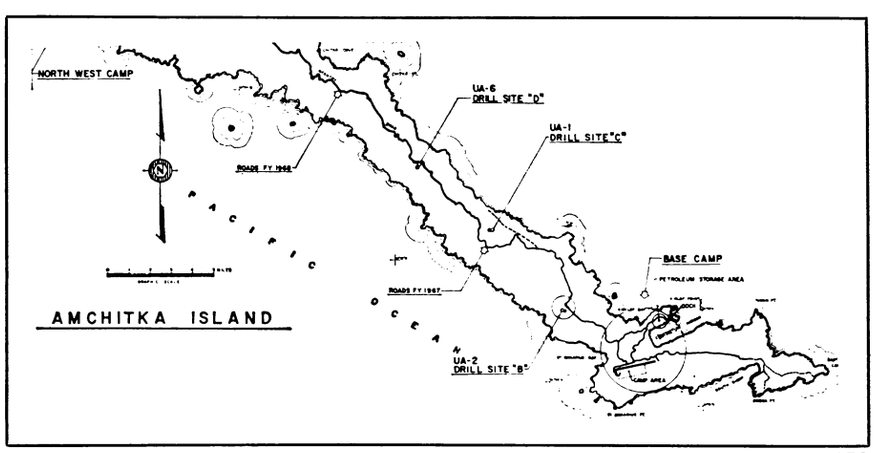
Many of the deaths from the Alaska earthquake were caused by the fast-moving tsunamis.

Looking at this new evidence, there still appears to be no systematic way to evaluate the danger involved in setting off successively larger nuclear explosions at Amchitka.

"The present level of understanding of seismic phenomena makes it difficult, if not impossible, to evaluate quantitatively the risks of conducting large underground tests in seismic regions," states the report of a panel on the safety of underground testing headed by Dr. Kenneth S. Pitzer of Stanford University. But it was studies such as these that led the Pitzer panel to voice serious concern about the earthquake possibilities following blasts at Amchitka. "The risk seems to be small but not insignificant since the consequences of accidentally releasing a large amount of tectonic strain energy could be extremely serious," it contends. "After much study we might a few years from now be able to say there is a one in one hundred chance or one in a million chance of something happening," says Dr. Brune. "Then if we could rate the risks of earthquakes we could compare them with other risks, and with the advantages. But now the public is asked to take this risk without knowing what it is . . ."

The successful detonation of the first nuclear device at Amchitka without incident, or "just as we predicted," as the Atomic Energy Commission put it, should intensify, not moderate, the debate about the test series, says Dr. Gordon J. F. MacDonald of the University of California at Santa Barbara. He was a member of the Pitzer panel.

"It may be that the energy stored in the ground beneath the test site isn't great enough to be released by the blasts," he says. "But the information about Amchitka is very sketchy, and I don't think the evidence is in either way." □



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MAN-MOUSE HYBRID

Mapping the genes

Maps of chromosomes already exist for bacterial genes, forming the intellectual backbone of some important genetic concepts. Gene mapping, for example, made possible the Nobel Prize-winning Jacob-Monod hypothesis that there are two classes of genes: one determining the amino acid sequence and hence structure of proteins and another controlling the function of those structural genes. Likewise, the operon theory that genes sitting side by side on a single chromosome operate as a unit depended on chromosomal maps.

Now, from the union of man and mouse, geneticists are compiling an atlas of human genes. Within four or five years, Dr. Frank H. Ruddle of Yale University predicts, it will be possible to draw maps of each of man's 23 pairs of chromosomes, at least outlining the geographical location of specific genes for specific human traits.

And, though Dr. Ruddle and his colleagues have little understanding of the mechanism of hybridization, they foresee additional implications not only for genetic counseling, but for cancer research as well.

Hybrid cells are an essential and simple tool with which to approach genetic mapmaking, Dr. Ruddle told the American Society of Human Genetics meeting in San Francisco last week, because they possess three special attributes:

- Human and mouse enzymes that

Dr. Conover

A hybrid—the U-shaped are mouse chromosomes, the X-shaped, human.

function alike differ biochemically in their physical properties. Thus, human lactate dehydrogenase (LDH), an enzyme important in the metabolism of lactic acid, can be distinguished from mouse LDH by simple laboratory tests.

■ Human and mouse chromosomes differ in their size, shape and biophysical properties, and it is therefore possible to look at a hybrid cell and tell how many human and how many mouse chromosomes are present.

■ In man-mouse hybrids, human chromosomes are preferentially and randomly lost. Therefore, a hybrid cell will contain all of the chromosomes from the original mouse cell but only some of the chromosomes from the human cells, usually no more than twelve, and each hybrid will not necessarily contain the same ones.

Chromosomes hold the genes that code for the production of enzymes. Because a hybrid cell contains all the mouse chromosomes, it should be able to make any mouse enzyme a mouse can. But because it contains only some human chromosomes, it will produce only those human enzymes coded for by the specific genes on the chromosomes that are there. Knowing this, scientists select an enzyme or two common to man and mouse, hybridize cells and examine the results.

Using this system, now about two years old, Dr. Ruddle has assigned the approximate location of the gene for LDH. Dr. James H. Conover of the Mount Sinai School of Medicine in New York reported experiments with two other enzymes: phosphoglucomutase, essential to the metabolism of sugar, and adenylate kinase, active in nucleic acid metabolism.

The first man-mouse hybrid was created in 1967 by Dr. Howard Green of New York University. To produce one, selected human and mouse cells are placed together in an ordinary culture medium where they live for four days. During this time, about 5 to 10 percent of those cells fuse by some mechanism only vaguely understood. Then the cells are transferred to another medium especially designed to kill off the parent cells, leaving only colonies of hybrids that can be seen with the naked eye.

These colonies are then separated from each other and placed in cultures where they clone, reproducing exact replicas of themselves. This process continues for a few days until there are enough cells to analyze for chromosome content and enzyme production. The clones contain neither the same nor the same number of human chromosomes.

Once each clone is analyzed, comparative studies ensue. First, the researchers determine which of the clones of hybrid cells contain the human form of the enzyme they are looking for. Then they look at the chromosome present in those hybrids. Human chromosomes, on the basis of their size and shape, are classed in groups designated A through F, plus the X and Y sex chromosomes.

Dr. Ruddle, working with Dr. Charlotte Boone, was concerned with LDH production. Each hybrid that contained LDH, he found, also contained one C-group chromosome. None of the hybrids missing LDH contained a chromosome from this group. Therefore, he concluded, the gene for LDH resides on a C-group chromosome, speculatively, number 11.

His LDH study was complicated by the fact that this enzyme is really a composite product of two genes. One codes for the production of a sequence of amino acids called the A subunit; another for an amino acid subunit called B.

To complicate matters still further, the B subunits of human and mouse LDH turned out to be indistinguishable by standard laboratory identification tests. In order to determine whether the gene for subunit A and the gene for subunit B reside on the same chromosome, it was necessary to find an individual whose LDH was made up of a B chain of amino acids that varied from the normal human enzyme, so that it could be distinguished from the mouse enzyme.

This required screening 5,000 newborns until a variant was found—a process that took a year. Hybrid studies with cells from mice and that individual showed that the two genes are not on the same chromosome.

In similar experiments with man-mouse cells, Dr. Conover finds preliminary evidence that the genes for phosphoglucomutase also are located on C-group chromosomes. None of his hybrid cells contained adenylate kinase (AK), the other enzyme he hoped to identify; he therefore concludes, by the process of elimination, that the AK gene is not located on any chromosomes identified in his hybrids.

"One mystery in all of this," Dr. Conover says, "is the fact that only a few chromosomes exist in any hybrid cells and the even more perplexing fact that as the hybrids divide and divide from generation to generation, human chromosomes are gradually lost, so that eventually we're back with a pure mouse cell."

While chromosome mapping is the immediate aim of this type of research—Dr. Ruddle speculates it may reveal information about the mechanisms controlling the complex pathways through which enzymes conduct biochemical reactions—Dr. Conover suggests it may eventually be important in genetic counseling. If scientists knew which genes code for specific enzymes and where they are located, they could test for their presence or absence in the cells of parents and be able to tell them whether they are likely to bear a child with a genetic defect.

In another vein, two British researchers recently proposed that hybrid cells might be of therapeutic use in fighting cancer. Drs. John Watkins and Louise Chen of Oxford University reported that when they hybridized mouse tumor cells with hamster cells and injected the hybrid line back into the cancer-stricken mouse, its tumor regressed (SN: 10/4, p. 306). Presumably, antigens on the hamster cells stimulated an immune response in the mouse that was able to wipe out both the mouse tumor and the foreign hamster cells. Participants at the San Francisco genetics meeting termed this approach "fascinating," but cautioned that a significant number of further experiments will have to be completed before it is possible to judge whether it is really practical. □