terslip finally arrives at the next stuck patch, adds additional stress to the patch, and, if the patch is near enough to failure, triggers its rupture. Once gradually increased stress had brought most of the patches near failure, the failure of one would trigger a cluster of failures, as seems to have happened three times on the Calaveras.

"We were about to send the paper out [to the *Journal of Geophysical Research*] when we had this 4.8," recalls Oppenheimer. It broke a part of a fault segment farther south, one that they had assumed broke entirely in 1955. "The model is still appropriate," he says. "We're still waiting."

If the next Calaveras earthquake arrives at all as forecast, all eyes will be looking still farther northward. Activity on the Calaveras appears to jump to the Hayward fault, which cuts through the cities of Fremont, Hayward, Oakland, and Berkeley. It was a section of the Hayward that broke in 1868 in a magnitude 6.9 shock, preceded by a 10-year cluster of five events near the Calaveras. According to a state study, a magnitude 7.5 event, the largest credible rupture on the Hayward, might kill 1,500 to 4,500 persons, injure more than 50,000, and wreak social havoc among the 5 million residents of the area. ■ **RICHARD A. KERR**

AIDS Drugs—Coming But Not Here

The discovery that the AIDS virus can become resistant to AZT, the only drug currently approved by the U.S. Food and Drug Administration for combating it, has given increased impetus to efforts to expand the arsenal of AIDS drugs. It puts "tremendous pressure" on AIDS researchers to come up with alternatives for people who are failing on AZT, says Jerome Groopman of New England Deaconess Hospital in Boston.

A major effort is already under way. The National Institutes of Health will spend about $90 million on AIDS drug research in fiscal 1989. The amount of spending by the drug industry is not available, but nearly 60 companies now have AIDS drugs in various stages of development, according to figures compiled by the Pharmaceutical Manufacturers Association. None of the new drugs are likely to become widely available for at least a year or two, however.

The potential AIDS drugs being identified work in diverse ways, attacking the AIDS virus at several points in its life cycle. This meets the general goal of developing drugs with different modes of action that can be used in combination. Such combination therapies should help to prevent the development of drug resistance by the AIDS virus, and may also give better control of the virus. "We're going to have to have alphabet soup to treat this disease," says John McGowan of the AIDS Program of the National Institute of Allergy and Infectious Diseases.

The reverse transcriptase inhibitors—the "sons of AZT" they might be called—are among the most advanced of the new AIDS drugs. Reverse transcriptase is an enzyme that copies the viral genome, which consists of RNA, into DNA, an essential early step in AIDS virus reproduction. AZT essentially tricks the reverse transcriptase into terminating DNA synthesis.

Some half-dozen additional inhibitors of reverse transcriptase are now in or are entering clinical trials (see table). The furthest along of these is ddC (for dideoxycytidine), a product of Hoffmann–La Roche, Inc., of Nutley, New Jersey, which is progressing from phase II to phase III clinical testing.

Phase I trials determine the maximum drug doses that patients can take without intolerable side effects, and phase II trials begin to assess a drug's effectiveness in a relatively small number of patients. For ddC, the early trials have shown that AIDS patients can tolerate doses that appear to reduce AIDS virus reproduction.

Phase III testing to assess ddC's efficacy in AIDS patients will begin in a few months if all goes well, says Thomas Merigan of Stanford University Medical School, who chairs the Primary Infection Committee of the AIDS Clinical Trials group. Meanwhile, the drug is being tested in combination with AZT therapy.

Other potential AIDS drugs act by preventing the AIDS virus entry into cells. These include the protein CD4, a product of recombinant DNA technology. CD4 is a soluble form of the receptor to which the AIDS virus must bind in order to infect cells. Injecting the protein into the bloodstream may, the theory goes, tie up the virus and prevent its spread in the body. Phase I trials of CD4 are under way. Researchers are also trying to make the protein more resistant to degradation and linking it to toxins that could destroy virus-infected cells.

Dextran sulfate, which many AIDS patients have been acquiring from Japan and taking on their own, also inhibits AIDS virus uptake in laboratory tests. Clinical trials to date, however, have not found any therapeutic benefits when the drug is taken orally, apparently because it is not absorbed from the digestive tract.

A third category of drugs acts at the end of the viral life cycle, inhibiting the assembly or maturation of the viral particles. Castanospermine, a product of the Australian chestnut tree, belongs to this category. A phase I trial of a castanospermine derivative (SC-48334) made by G. D. Searle & Company is to begin in the next few months.

Hypericin, an antiviral chemical from the common flowering plant Saint-John's-wort, apparently also inhibits a late step in AIDS virus maturation in laboratory tests. Daniel Meruelo of New York University Medical Center, who is studying hypericin, says that discussions with the FDA about putting hypericin into clinical trials will be held later this spring but it will be some weeks before any decisions are made.

Researchers are also looking for compounds that inhibit the viral protease, an enzyme that releases the individual proteins from which the virus is assembled. Another strategy is to try to prevent synthesis of the viral proteins in the first place by tying up the messenger RNAs that direct protein synthesis. Neither of these approaches is ready yet for clinical testing.

Finally, several natural human products that bolster antiviral defenses or the immune system are in clinical trials. These include Imreg-1, interleukin-2, and the virus-fighting interferons. Another protein, granulocyte-macrophage–colony stimulating factor, may be useful for counteracting AZT's toxic effects on the bone marrow, which prevent as many as 50% of AIDS patients from taking the drug. ■ **JEAN L. MARX**

A Few Major Contenders

Drug/Source	Clinical Status	Mode of Action
AZT Burroughs Wellcome Co.	Approved by FDA	
ddC Hoffmann–La Roche, Inc.	Phase II trials	Reverse transcription inhibitor (suppresses viral DNA synthesis)
d4T, ddI, ddA Bristol-Myers Company	Phase I trials	
AZDU Triton Bioscience	Trial to begin in a few months	
Carbovir National Cancer Institute	Trial to begin in early 1990	
CD4 Biogen, Inc. Genentech, Inc.	Phase I trials	Inhibits viral entry into cells
SC-48334 G. D. Searle & Company	Trial to begin in a few months	Inhibits viral maturation