of a chimney by a deep-sea vehicle steered by remote control from the surface; once dropped, cables inside the device were

Viruses

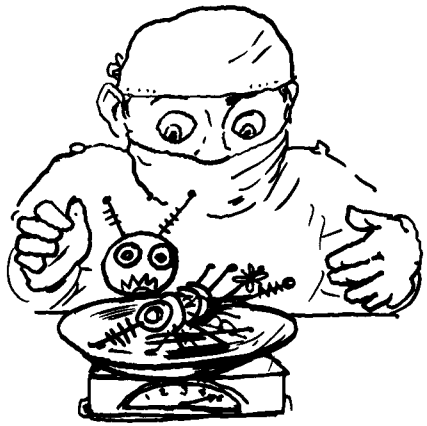
Hunt the mutant

WHEN panic struck Hong Kong last year after a mysterious new strain of a bird virus started to infect people with chicken flu, virologists searched frantically through the bug's genetic material to discover how it had changed. But combing through the thousands of genetic letters that make up a virus's genome is slow work. Hence the interest in a new, quick method for identifying mutants, described in this week's *Proceedings of the National Academy of Sciences*. It is based on a simple premise: the proteins that a mutant strain produces do not weigh the same as those made by the original virus.

Physicists have long been telling one compound from another by comparing weights. To do this, a substance is vaporised by heating, and then bombarded with electrons to give it a charge, or "ionise" it. The ions then go into one end of a mass spectrometer, where a combination of electric and magnetic fields accelerate them. How fast the ions go depends on their weight: heavy particles move more sluggishly than light ones, so measuring how long a particle stays in flight reveals its weight.

For a long time, biological molecules could not be analysed in this way because they tend to be destroyed by heat. But about ten years ago, a technique was developed to vaporise and ionise these molecules too, but without heating them directly. Now, Gary Siuzdak and Kathleen Lewis, molecular biologists at the Scripps Research Institute, in California, and their colleagues there and at Purdue University, in Indiana, have applied this technique to viruses. In doing so, they have stumbled on a remarkably swift and accurate method for spotting mutations.

Whenever a mutation occurs, it changes the virus's genetic message. The old way of looking for that meant searching directly—and slowly—for the change. But when the virus produces protein, a troublesome mutation results in a change to the amino acid sequence that makes up the protein. This



means that rather than looking for changes in the genetic material, one can look for changes in the proteins. This is what Dr Siuzdak and his colleagues did.

As their guinea pigs, they took the tobacco mosaic virus and the human rhinovirus (responsible for colds) as well as mutant versions of both; and they attacked both the normal virus and the mutant with a digestive enzyme. The enzyme breaks up a virus's outer protein envelope into a mixture of mini-proteins known as peptides. Each peptide has a weight that depends on whether it was produced from the original or the mutant virus.

By feeding the entire mixture into the mass spectrometer, the researchers can quickly spot a peptide produced by a mutant. And since biologists already know which part of the genome makes which peptide, this approach immediately shows whereabouts in the genome the mutation is. So only a small part of the genome has to be sequenced directly. If the difference in weight matches one particular amino acid, gene-sequencing can be bypassed altogether. Mutants that would have taken days to identify using old methods were spotted by Dr Siuzdak's group within 20 minutes.

Dr Siuzdak's team has already formed collaborations to study mutant forms of other viruses, including hepatitis B and HIV, the virus that causes AIDS. The likelihood that a mutant protein can slip through unnoticed is small: the spectrometer can tell apart proteins that differ by less than a tenth of a proton mass in weight. For mutants, size might not matter, but weight certainly does.