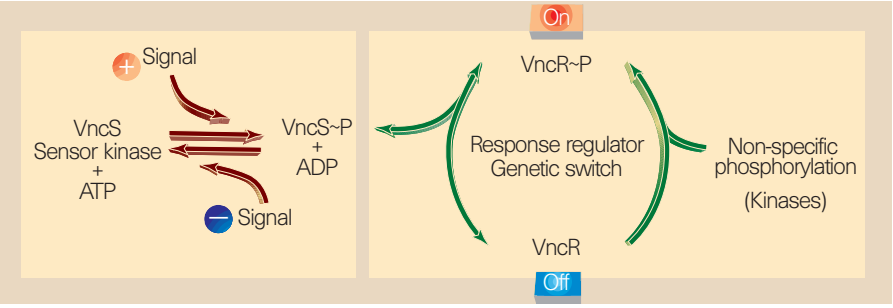

Figure 1 **A two-component signal-transduction system. Environmental signals regulate the addition of a phosphoryl group (P) to the sensor kinase (VncS). This, in turn, controls whether the response regulator (VncR) is on or off. The sensor kinase can turn the response regulator off by removing its phosphoryl group in the absence of the environmental signal. It can also eliminate activation by non-specific phosphorylation of the response regulator in this way. Novak *et al.*[3] have found that multiple-antibiotic-resistant bacteria have mutations in such a two-component system. When VncR is phosphorylated (active), genes that are turned on in response to antibiotics — and kill the bacteria — are switched off. Mutations in the VncS component mean that VncR cannot be switched off, with the result that the death-promoting genes remain inactive.**

ple-antibiotic-tolerant pneumococci selectively persist in experimental meningitis. Moreover, in a controlled comparison, the authors found that these mutants are better able to take up DNA than normal cells. This raises the real possibility that, through DNA uptake and recombination in nature, new strains of pneumococci will continue to arise that are increasingly difficult to treat with existing drugs.

Novak and colleagues have also pinned down the genetic basis for the vancomycin tolerance — specific mutation of a two-component signal-transduction system. Two-component systems control a variety of responses in bacteria and lower eukaryotes[5]. These signal-transduction systems allow the microorganisms to sense their environment and to respond to this by adjusting gene expression. The environmental stimulus is recognized by a specific 'sensor' kinase, which, on binding the stimulating molecule, adds a phosphoryl group to itself (autophosphorylation). Each sensor kinase in the cell is paired with a specific response-regulator protein that controls the expression of a unique group of genes. Transfer of the phosphoryl group from the stimulated kinase to the response regulator activates this switch function, and the response regulator then turns gene function either on or off.

This genetic switch is active as long as the stimulating molecule is present and the sensor kinase remains phosphorylated. But if the stimulating molecule disappears, the process is reversed and the switch is turned off. The forward and reverse reactions combine to fine-tune the levels of activated response regulators present to the level of the stimulating molecule. The reverse reaction can also switch off the response regulator if it is activated, not by the sensor, but non-specifically by other kinases or by small molecules such as acetyl phosphate. Stimulating molecules may ultimately promote either phosphorylation or dephosphorylation of the response regulator, depending on how a particular system is configured.

Novak and colleagues[3] found that experimentally induced penicillin-tolerant *S. pneumoniae* mutants, which are also tolerant to structurally unrelated antibiotics such as vancomycin, aminoglycosides and quinolones, contain mutations in a two-component system (Fig. 1). The bacteria became tolerant when the authors inactivated the sensor kinase (VncS) of this system, but not when they turned off its response regulator (VncR). Consistent with this, the authors detected vancomycin-tolerant clinical *S. pneumoniae* isolates with mutations in the VncS sensor kinase. These data indicate that, in the 'on', phosphorylated mode, the VncR response regulator represses some of the genes required for antibiotic-induced death. Normally, exposure to antibiotics causes VncS to remove the phosphoryl group from VncR, returning it to the 'off' mode and allowing these genes to be expressed. But once VncR is activated (by, say, non-specific phosphorylation in the cell), it cannot then be inactivated (dephosphorylated) without functional VncS, so the antibiotic-induced genes will remain switched off.

The data also suggest that, on exposure to all of the antibiotics tested, *S. pneumoniae* produces a common signalling substance that is sensed by VncS, triggering cell death. This signalling substance could come from bacterial cell-wall precursors that cannot be incorporated into the cell wall in the presence of antibiotic. Or, it may originate from other pathways affected, directly or indirectly, by antibiotics. Whatever the mechanism, by understanding the connection between sensing the triggering molecule, and the pathway by which cell death is induced, we may be able to develop new approaches for treating increasingly common and problematic multiple-antibiotic-resistant infections[6]. For it is now clear that signal

100 YEARS AGO

The season of strawberries is at hand, but doctors are full of fads, and for the most part forbid them to the gouty. Let me put heart into those unfortunate persons to withstand a cruel medical tyranny by quoting the experiences of the great Linnæus. … in 1750 he was attacked so severely by sciatica that he could hardly make his way home. The pain kept him awake during a whole week. He asked for opium, but a friend dissuaded it. Then his wife suggested "Won't you eat strawberries?" It was the season for them. Linnæus, in the spirit of an experimental philosopher, replied, "*tentabo* – I will make the trial." He did so, and quickly fell into a sweet sleep that lasted two hours, and when he awoke the pain had sensibly diminished. He asked whether there were any strawberries left: there were some, and he eat them all. Then he slept till morning. … What lucrative schemes are suggested by this narrative. Why should gouty persons drink nasty waters, at stuffy foreign Spas, when strawberry gardens abound in England? Let enthusiastic young doctors throw heart and soul into the new system.
From *Nature* 8 June 1899.

50 YEARS AGO

In November 1948, we found at Swartkrans while excavating a new site in co-operation with the California University Expedition a lower jaw with very large molar teeth. I called it *Paranthropus crassidens*. Not only did we find the imperfect jaw of a young male with three upper teeth, but also some months later the snout of what appeared to be a female. The upper incisors and canine are typically human. Last month, while I was in America, my assistant, Mr. John T. Robinson, discovered an almost complete huge jaw with most of the teeth. … The jaw is really enormous – very considerably larger than that of Heidelberg man. The molar teeth are very large, but the canines and incisors remarkably small. Another remarkable feature about the jaw is that it has a rudiment of a chin. The ascending ramus is also very high and large. Mr. Robinson has also got a part of the face with the nearly complete palate. This shows that the face is almost orthognathous. We must, I think, conclude that the brain was very large.
From *Nature* 11 June 1949.