Investigating bacterial communication
Discovering bacterial communication

Roger Finch
Over the last 50 or 60 years we've had an increasing number of antibiotics available for treating infections in man and animals, but over those years there's been a gradual erosion of their effectiveness.

Paul Williams
One of the scourges of the end of the twentieth century is that so many different bacteria have become resistant not just to one class of antibiotic, but to multiple classes. And therefore the race is on to try to keep one step ahead of the bacteria.

Barrie Bycroft
The approach that we've used for almost the past century has involved mechanisms that could be described as putting domestos in a pill, so that we kill all known bacteria stone dead.

Roger Finch
We're reaching to the point where, as prescribing doctors, we are increasingly concerned whether we are going to choose the right drug when initially faced with our patients

Narrator
But bacterial communication may hold the key to a completely new kind of therapy. It all started with some research into conventional antibiotics.

Paul Williams
Something like ten years ago now, I came to Nottingham to join the School of Pharmaceutical Sciences, and one of my colleagues Barrie Bycroft was particularly interested in a group of beta lactone antibiotics. These are very much like the penicillins, and the reason he was interested in them was because as a family they are very potent antibiotics but they haven't been well developed by the pharmaceutical industry.

Barrie Bycroft
What we stumbled on was a regulatory mechanism which was used by the organism to express the antibiotics.

Paul Williams
…can you see the zone of inhibition right in the colony killing off the ecoli that we've seeded in the plate

Narrator
The antibiotic is called a Carba Penems. The bacterium producing it is Erwinia

Paul Williams
We used some standard genetic techniques to make mutants of Erwinia which could no longer produce the antibiotic.

Paul Williams
…and look what we've got on this plate. We've managed to find six mutants that can't make the antibiotic any more. Here you can see three that are still making the antibiotic, you can still see the halos, and then we've got one, two, three, four, five, six that can no longer make the antibiotic.

Paul Williams

When we'd generated sufficient mutants, we decided the easiest thing to do was to mix different mutants together

Narrator
The scientists were hoping that some combinations of mutations would cancel each other out.

If this happened, it would help them to understand how the antibiotic was made.

Paul Williams
None of these mutants can make the antibiotic themselves. If you mix them back together, you find the antibiotic's being produced again, you're pretty sure that one of those mutants is making a substance which it's secreting; the other mutant is taking it and using it to produce the completed antibiotic.

Narrator
Identifying such a substance would be the first step towards engineering a new class of antibiotics. The plates would show whether there was any such chemical there.

Paul Williams
Hey, Miguel, come and have a look at this - it's worked!

Miguel Camara
“That's brilliant!”

Paul Williams
We’ve actually got cross feeding. Mutant 2 is being cross fed by super natent from Number 1 We’ve got it - it’s just what we’ve been looking for.

Paul Williams
So we spent about six months trying to figure out what this molecule actually was.

Narrator
What they were expecting to find was a molecule resembling an antibiotic. What they actually found was an unrelated molecule called OHHL.

It was quite a disappointment.

Paul Williams
We had to agree that yep, this molecule could not be possibly part of a biosynthetic pathway, it just did not look like a carbapenem at all. So we had to concede that maybe no BMW in the carpark, we wouldn't be getting the huge pharmaceutical industry budget to develop this family, we'd actually gone in the wrong direction.

Narrator
But they still had the molecule.

Paul Williams
Then we sat back and thought well, maybe this is very interesting because the molecule that we had, well, was it a known molecule? It was an interesting molecule, so then what we did was go to the library, and we discovered that my goodness, this compound was a known compound, it was out there, it was known, and it had something to do with deep sea bioluminescent organisms.

Caption 1:
Inside bioluminescent fish or squid a bacteruium called Vibrio fischeri uses Paul's chemical as a signal to light up. This happens only when the bacterium is in a colony, packed inside a host.

Caption 2:
The bacteria seemed to be behaving like the directors of a company. They can't act until they've reached a quorum. In effect, the bacteria use chemical signaling to count heads.

Narrator:
In bioluminescence, this process was already understood. Scientists called it "Quorum Sensing", as it reminded them of boardroom protocol.

One particular research group had studied it in detail. Amazingly, they were on the very same campus as Barrie and Paul.

The leader of the group was Professor Gordon Stewart. In October 1990 there was a meeting of minds.

Paul Williams
I went up to Gordon, I didn't know him very well at the time, and I said Professor Stewart, I understand you work on these bioluminescent organisms. How would you respond if I were to tell you that we've discovered the same signal molecule that switches on and off bioluminescence in marine organisms in a land-loving plant pathogen called Erwinia. And it controls carbopenem, antibiotic synthesis, what would you say? And I had to pick him up off the floor. Because this is wonderful, he said, this is marvelous, this is something that had been a holy grail.

Narrator
Gordon and his colleagues had long believed that other bacteria must use quorum sensing. The system was so elegant, they thought, it couldn't be unique. But for the wider scientific community the idea was a shock.

Barrie Bycroft
Why it was a surprise was that as experimental scientists, we use microorganisms in a laboratory, and we don't necessarily observe them too much in their natural environment.

Paul Williams
Our interests were in big molecules, macromolecules, proteins and nucleic acids. We didn't really think about the small organic molecules that we were throwing out. And so we'd been throwing the baby out with the bath water essentially for a long time.