> *“40 years of progress and fungicide resistance strategies have stayed the same.”*

Chasing the Red Queen

Technical
Fungicide resistance

After more than 40 years in plant pathology, a career which Bill Clark describes as often ‘squatting in crops’, he finally hung up his wellies at the end of July. Earlier that month he sat down with *CPM* to reflect on what’s changed in that time, but most poignantly, what hasn’t..

By Lucy de la Pasture

The new NIAB HQ in Cambridge, just a stone’s throw from its original location in Lawrence Weaver Way, opened just before the first lockdown was announced in March 2020. Even as the country was opening back up in July this year, the offices still were eerily empty — much to the frustration of its technical director Bill Clark, who was hoping to experience the buzz the purpose-built hive had been designed to foster.

In just a fortnight Bill was due to hand over the pathology reins at NIAB to Dr Aoife O’Driscoll but his passion for his subject is still very much in evidence as he considers how things have changed during the course of his career. He says it’s been earmarked by ‘the cavalry always coming over the hill,’ but reflects that the cavalry has also been part of the disease resistance problem.

Path into pathology

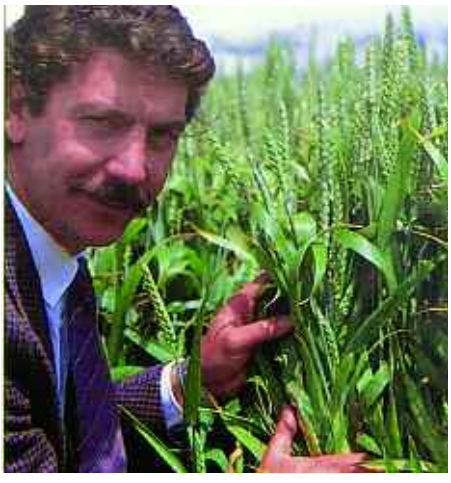
Bill came from a farming background, having grown up on farm in Durham. It was as a boy of about 10 years old that his path into crop pathology was set. “There was a problem on the farm with swedes which had hollow hearts. I remember a NAAS (National Agricultural Advisory Service) advisor arriving and cutting open the swedes. He diagnosed a boron deficiency and I was completely bowled over by this guy because he was so knowledgeable. It was probably then that I decided what I wanted to do,” he recalls.

At university Bill studied zoology and botany, soon transferring to straight botany where he took all the pathology options to end up with a degree in plant pathology. But he found he couldn’t link the science he’d been taught at university with the farming he’d grown up with, so he went to Harper Adams as a post-graduate and that connected the two things together.

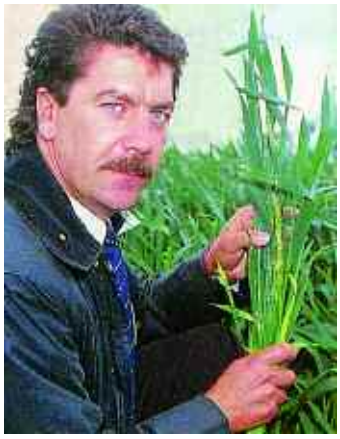
Joining ADAS was exactly what Bill did in 1977 when he took up the post of plant pathologist at ADAS Reading. He then moved to ADAS Leeds in 1979, where he was working with protected crops at Stockbridge House, before moving to the Newcastle office in 1983. In 1987 Bill moved to Cambridge where he spent the next 20 years as a specialist cereal plant pathologist and national cereal pathologist at Boxworth.

In 2007 Bill moved on to become director of Broom’s Barn Research Centre, where he remained for four years before taking his current position at NIAB in 2012. Looking back over his career Bill wryly says it seems that “the more things change, the more they stay the same.”

To illustrate the point he picks up the ▸



Fungicide resistance messages were beginning to be refined in the late 1980s, says Bill Clark (pictured in 1988).



Bill (pictured in 1991) says that in the 1990s straight actives were still being recommended in spite of the warnings about resistance.

▸ 1977 copy of ADAS's booklet on cereal diseases and highlights that at the start of his career there was absolutely no mention of fungicide resistance.

"We were blithely recommending MBCs — carbendazim, maneb etc. Fungicide resistance wasn't a story — it wasn't even talked about. A lot of the recommendations were for straight products."

Bill recalls that one of the earliest resistances the ADAS team found was MBC resistance in eyespot and DuPont went mad at them. "They threatened to sue us for even talking about resistance," he says.

"In 1977, there was hardly any mention of *Septoria tritici*, it was all about *S. nodorum*. *S. tritici* was described as 'mainly a disease of seedlings'. Another thing that was interesting was the price of fungicides. It cost £10/ha for carbendazim (Delsene M), which is equivalent to £56 today, so they were very expensive which is partly why they weren't that widely used.

"At that time, we were getting up to six new fungicides a year so there was no shortage of new chemistry. But the industry knew there were some problems even though they were pushing back against it."

The Fungicide Resistance Action Committee (FRAC) was set up in 1981, which was the first time there was an international agchem group to investigate resistance and how to manage it, continues Bill. "The problem at the time was the pace of active ingredients coming to the market — every time one failed there was another one round the corner. So where there was a problem, the cavalry would come charging over the hill in the form of a new product. So resistance wasn't taken seriously."

By 1982 a whole section on fungicide resistance appeared in the ADAS booklet for the first time. "In five years it had gone from not being talked about to a major national and international issue for all the manufacturers. What is sobering to me is that you could lift the wording in that ADAS booklet and put todays date on it — it reads exactly the same."

Bill was part of the cereal pathology group which produced the advice, which was to use non-chemical means such as resistant varieties as well as different modes of action and fungicide mixtures to control diseases — all things you could re-present today, he says.

"I don't know whether it's sad or just strange that we haven't really moved on very much in terms of our advice about how to manage fungicide resistance. It's become more urgent now because we don't have new actives coming along all the time, so we're having to take it more seriously.

Molecular biology has revealed that the septoria pathogen has developed multiple mutations in the same enzyme without losing any fitness, which is remarkable for a fungus.

In the late 1970's, Septoria tritici was only a problem in seedling wheat and S. nodorum was the dominant species.

Straight actives

"It was clearly of importance back then and strategies were being put into place, but I don't think the industry really took much notice. A lot of straight actives were still being recommended so we were sailing very close to the wind. We got through the 1980s simply because we had lots of new chemistry."

Bill says it's much the same story now. "We say you should be mixing products but there's a cost to that. So is it your responsibility as an individual farmer or is it the industry's responsibility? I remember talking about it at the time, that manufacturers should be producing properly formulated mixtures but commercial pressures then, as they are now, prevent them from doing it — the best co-form partners are usually somebody else's."

In the UK there's another factor which contributes to the problem we have with resistance, says Bill. "Distributor pressure forces manufacturers to produce single actives, with the agreement they'll be used in mixtures. It hands over the responsibility to the advisor to make the right decision and often they're not well informed enough about whether the products to be mixed are well matched at the rates they're being used at, in terms of their systemicity, persistence and kinetics.

"40 years of progress and fungicide resistance strategies have stayed the same," reflects Bill.

"In 1985 we reported septoria resistance to MBCs, which were single site MoA being used as straights so it was almost inevitable. But even though we were reporting this, we were saying 'there are other products available', so there was no alarm and no change in behaviour. Triazoles were being used as straights, even though we'd known there was a resistance problem with MBCs for three years. We hadn't learnt our lesson."

By 1986 the messages were refined a little — there was more of a push on using multisites, such as captafol, chlorothalonil, mancozeb, thiram, mercury (seed dressings) — but something that was overlooked then, and still is today, is that fungicides used in a mixture should be equally effective, he highlights.

"People say it but don't put it into practice. This is the problem with old multisites — if you're mixing a protectant product that's not systemic with something that is systemic and eradicant, then they're not well-matched partners. They're not protecting each other.

"And now in France we see sulphur being recommended again, forty years on. Talk about back to the future, it wasn't that ▸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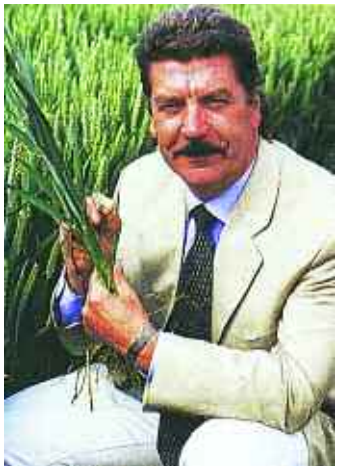

By 2004 the strobilurin group of chemistry had almost entirely broken down for septoria control but still the cavalry were coming over the hill, says Bill (pictured in 2004).

▸ good then and it isn't that good now."

And then the stobilurins came on the scene. "Bravo (chlorothalonil) wasn't being used when the strobilurins came in and I think that was part of the problem," he says. "They went very quickly and once the strobs stopped working, people went back to using Bravo."

In 2004, Bill was doing a lot of work with BASF on the physiological effects of strobilurins. Comet (pyraclostrobin) was still giving 40-50% control of septoria even though it was affected by the G143 mutation, so Bill was keen to find out why.

"Pyraclostrobin was always the most effective at prolonging green leaf area and had ethylene-inhibition effects, so delayed senescence. It had direct physiological effects on plants. It's not very effective anymore on septoria, we looked at this recently and found around 10% control, but strobs can still give useful greening effects if used for rust control later in the season."

Bravo was helping to prop up the dwindling chemistry as efficacy to the single sites continued to drift, says Bill (pictured in 2012).

Bill has another bug bear that has haunted his career and he points to a story in the farming press, published in 2004, where an agchem resistance specialist was saying that using low rates causes resistance. "That was and has been the story for a very long time — and it's a myth," says Bill. "It's been a consistent message, but it became very clear in the research that it was high rates that were causing more resistance development. The only time low rates cause resistance is if you use them multiple times — so three low doses will encourage resistance, but three high doses will select for even more resistance."

Bill says looking back, it's a salutary tale. "You'd think at a time when we'd seen MBC resistance, the strobs go and the triazoles drifting, that straights wouldn't be being used. But we were all trying to convince ourselves that the drift was slow and wasn't really anything to worry about. It was all happening and yet nothing really changed — recommendations were still the same."

So in 2006 at the AAB Conference Bill presented a paper titled 'Are we winning the battle but losing the war?'

"I wrote a pretty damning thing in the paper — 'there's no anti-resistance strategy that will prevent resistance, all we're doing is delaying it'. It was a true statement and inevitable because all of the products coming through were single sites, and it's even more true today. Modern actives are all single site, and we don't have varieties with durable resistances — varieties come and go very quickly on the AHDB Recommended List."

In that paper Bill also wrote that broad spectrum multisites have been 'invaluable', but he expressed concern that they were just concealing the weaknesses of their partners.

"Everyone was mixing with Bravo and all looked well in the field but, underlying that, we were still seeing a drift in the efficacy of its single-site fungicide partners. Now Bravo has disappeared it's highlighting the weaknesses of some of the products we're using. Bravo was whywe were winning the battle but, in the longer-term, losing the war as the single sites were eroded."

Cavalry still coming

As things happen, the latest in this long story is that more cavalry are coming over the hill, says Bill. "New MoAs are coming but we also have new azole chemistry such as Revysol (mefentrifluconazole) and a pipeline SDHI (Adepidyn) which are coming into a population that's already selected for septoria resistance to both groups. That's a challenging environment to bring new products into.

"It's clear septoria is incredibly malleable. You never have thought you'd find a fungus with so many mutations in an enzyme and that it could still be performing normally."

But the cavalry has turned up with Inatreq, a new MoA, but it's at a high risk of developing resistance, he explains. "It's a fantastic product but it's desperately in need of a good mixture partner — the best partner would be Revysol but that's not commercially acceptable to the manufacturers.

Bill is a little dismayed at the past forty years of 'progress'. "We still have triazoles but we're losing them and even Revysol will drift in efficacy. The new SDHIs look great — Iblon and Adepidyn — but I talk about the 'Red Queen' effect, where we're running faster and faster, just to stand still. All they're doing is bringing in new products that are more effective but giving us the same level of control that we used to have when the older products first came in. We're on a very slippery slope.

The Cougar strain of S. tritici (left) has a different phenotype to 'normal' septoria and can be distinguished by its orangey colour and indistinct pycnidia.

"The Adepidyn I was looking at last week looked amazing. It really is the next generation and way better than bixafen and xemium. It's a completely different product but it's still an SDHI and it's coming into a septoria population that's already adapted a dozen different mutations, so it will go in time. Revysol basically just recovers all the eradicant activity we used to have with the triazoles.

"We have Inatreq — a brand new MoA and no selection for resistance but a very high-risk product so, unless it's really well protected, the inevitable will happen. And then the next cavalry over the hill will be BASF with metyltetraprole — which is a QoI, but it's a strob that's not affected by the G143 mutation."

So how do we stop this cycle? Bill believes that the industry will soon be in a position where it could properly look after chemistry using what he calls 'intelligent mixtures.'

"We have the tools but still have this problem that we don't have any inter-company cooperation. In a couple of

years we will have a triazole, a QiI, a QoI and an SDHI — four different MoAs. All well balanced in terms of their efficacy, their systemicity, their spectrum of activity — this is almost like the Holy Grail. We'll be able to mix two modes of action at T1 and use two different MoAs at T2, effectively using a MoA once per season and mixing it with a partner that will protect it. This is what we would have loved 40 years ago."

But there's a commercial problem to be solved if this is to become a reality, he acknowledges. "The trouble is that farmers would end up having to buy twin packs, splitting them, and mixing them together themselves. Again the commercial pressures will prevent people doing this. In a couple of years, we'll have these four MoA and that's it — there's not even cavalry over the next hill or even the hill beyond that. We have this opportunity to create intelligent mixtures but there's so much commercial pressure and that will break these products if we're not careful."

Even the cavalry arriving won't solve the other problem growers are facing — the breakdown of varietal resistance, says Bill. "Add in the issue with new strains of septoria — such as those found on Cougar a few years ago, which seem to be coming to the fore again — we think these have shorter latent periods in the susceptible varieties which makes timing really difficult. And none of these new products will make any difference, the issue they create is all about the timing of control."

He explains that 'normal' septoria may have a three-week latent period, or more on a resistant variety, which effectively gives a window of a week and a half to apply a fungicide at GS39 to control septoria on leaf two and the flag leaf.

"If like this year, when it was wet throughout May, and leaf two is becoming infected as it is emerging, by the time leaf one has fully emerged then the infection you're trying to control may be 10-14 days old. The Cougar strains seem to have shorter latent periods, giving you only about seven days to treat. That means a flag leaf spray is never going to work to control septoria on leaf two. You could put a full dose of any of these products and they will not control septoria beyond halfway through its latent period."

If the Cougar strains are widespread, and there are lots of varieties with it in the parentage on the RL, then they are all going to get more septoria than expected, says Bill. That means spray timings will have to change.

"In the 1970s/80s we talked about leaf layers and not T1/T2. It's more helpful to return to talking about leaf layers as each new layer will need protection with the Cougar strains. So the answer isn't in the can, even though we have much better products now, in a way nothing has changed because it's all about timing."

What can be done to make this situation more sustainable? Bill says we need better varieties. "We thought we had them, with varieties with 7 rating for septoria — but it's clear we lack resilience and require a more robust resistance."

Bill's final thoughts are thought provoking. "My whole career has been working on resistance and it's been the same thing, the cavalry coming over the hill. I genuinely believe we're at a stage where that's not going to happen — the cavalry is on furlough and they're not coming." ■

Bill says that after the remaining cavalry arrive over the next couple of years, there are no more back-ups in sight so these new actives must be stewarded by using intelligent mixtures.