Yield penalties of disease resistance in crops
James KM Brown

Recently, there have been rapid developments in understanding the costs of disease and pest resistance in model plants and their ecological relevance in wild plants. In crop plants, however, much (although not all) of our current understanding of costs of resistance must be inferred from research on model species. To determine the true costs of resistance in crops and the likely benefit of resistance genes in new cultivars, however, other aspects of the plant’s phenotype must be studied alongside resistance.

Introduction
Disease resistance is often assumed to be costly. Indeed, many traits that are associated with resistance to pathogens and herbivores reduce plant fitness, although others do not [1]. Research on costs of resistance is currently enjoying a surge of interest. This is particularly true of studies of the mechanisms underlying costs in model organisms, such as Arabidopsis, and their ecological significance in wild plants. Although crops have not been completely neglected, it is fair to describe research in this area as sporadic. There has long been evidence that disease resistance may affect crop performance [2], but several of the most informative experiments were done a decade or two ago and have not been properly followed up. In this review, therefore, although I cover research progress in the past year, I also attempt to identify critical areas where our knowledge or understanding is most seriously lacking.

I focus particularly on yield, the single most important indicator of crop performance. In a breeding programme, many factors must be weighed against one another, and disease resistance is rarely the most important. In the UK, for example, the key targets for wheat breeding are yield, quality and standing power, in that order. Disease resistance as a whole is no higher than fourth in a breeder’s list of priorities, whereas resistance to any one disease is simply one of several factors that must be considered when deciding whether or not to market a cultivar. If resistance has a substantial cost, therefore, it has commercial significance because it may hinder the more important objective of increasing yield.

Two useful, general reviews on costs of resistance have been written by Purinton [3], who focuses on the mechanisms of costs, and Bergersen and Purinton [1], who comprehensively review research published before 1995 on costs of resistance to pathogens, herbivores and herbicides. Bergersen and Purinton [1] emphasise studies in which the genetic background was controlled so that the effects of resistance (R) genes could be distinguished from those of other genes. They include meta-analyses of the influence of several factors on the ability of experiments to detect costs of resistance. Some caution should be exercised in this respect, because the unit of analysis was the research paper. Hence, four papers that reported a cost associated with the mlo gene in barley for resistance to powdery mildew (Blumeria graminis [syn. Erysiphe graminis] f. sp. hordei) [4–7] were treated as four separate data supporting the hypothesis that resistance is costly. In contrast, three papers in which no cost was associated with any of ten or more gene-for-gene (GFG) resistances to barley powdery mildew [5,8,9] were treated as just three data against that hypothesis.

Linkage or pleiotropy?
A direct effect of an R gene on yield implies an underlying mechanistic relationship. However, genes that are linked to an R gene may also affect yield and hence hamper the selection of commercially successful resistant cultivars. Such linkage is especially likely to create problems when the R gene has been introgressed from a wild relative of the crop. Under these circumstances, there is little recombination between the introgressed segment and the homoeologous segment in the crop species. It is generally only worthwhile for a breeder to analyse such a linkage and to try to break it when the yield penalty in the absence of the target pathogen or pest is commercially significant.

Wild-relative species are especially important in the breeding of wheat. In wheat, recombinants have been found in which the Pshl gene for resistance to eyespot (Tapesia spp., a stem-base disease) from the wild grass Aegilops ventricosa is no longer linked to a gene for reduced yield [10]. On the other hand, linkage between yield depression and the Lr9 R gene from Aegilops umbellulata, which confers resistance to wheat brown rust (also known as leaf rust [Puccinia triticina, syn. Puccinia recondita f. sp. tritici]), has not been broken [11]. Other R genes on introgressed segments that are associated with reduced yield are Wsm1 for resistance to wheat streak mosaic virus from Thinopyrum intermedium, which is associated with a mean yield reduction of...
21% [12•], and three genes for stem rust (Puccinia graminis f. sp. tritici) resistance, notably Sr26 from Agropyron elongatum, which has a 9% yield penalty [13]. Introgressed segments do not always incur a yield penalty. Another T. intermedium translocation, carrying resistance to barley yellow dwarf virus, conferred no significant reduction in grain yield, plant biomass or grain size (measured by thousand-grain weight [TGW]), of uninfected plants [14•]. Indeed, the 1RS chromosome arm from rye, which carries several disease resistances, is associated with increased yield even in the absence of disease [15]. Not all R genes that are linked to reduced yield have been introgressed from related wild species. In combination with other Lr genes, Lr34 from Frontana and other South American cultivars has provided durable resistance to brown rust of wheat but was associated with a reduction in grain yield of 6%, as well as with significant reductions in most of the yield components analysed [16]. In winter barley, the gene ym4 from the Croatian landrace Rugasa confers resistance to barley mild mosaic virus (BaMMV) and strain 1 of barley yellow mosaic virus (BaYMV-1). ym4 was associated with an average reduction in grain yield of 2% across eight trials [17]. It is not yet possible to determine, either in the case of Lr34 or in that of ym4, if the yield penalty is a direct effect of the R gene or an indirect cost of linked genes.

Transgenic plants may be used to distinguish the effects of linkage and pleiotropy and so to improve understanding of the mechanisms underlying costs of resistance [1]. Ideally, more than one insertion of a transgene should be used in such experiments in case the site of insertion has an effect on yield because of linkage to deleterious genes. Using this approach, Magg et al. [18•] showed that two insertions of the CryIA(b) gene, encoding an insecticidal toxin from Bacillus thuringiensis, had no significant effect on grain yield, grain dry matter or plant height in the absence of larvae of the European corn borer (Ostrinia nubilalis).

**Costs of disease escape**

A second indirect cost that is important in breeding concerns disease escape. Plant architecture and rate of development that are optimal for yield and agronomic performance may increase disease by promoting the spread of infection or the development of symptoms. A breeder therefore needs to balance the advantages of modifying these characters so as to escape disease against any reduction in yield or performance. The angle, length and separation of wheat leaves affect the net rate of short-distance dispersal of the splash-borne conidia of Mycosphaerella graminivora, which causes septoria tritici blotch. Long leaves that are close together tend to allow spores to be dispersed successfully between leaves and so increase disease [19]. Most UK breeders, however, prefer to select wheat lines that have short stems, which stay standing in wind and rain, and long leaves, which maximise the interception of sunlight. The date of crop maturity may also affect disease escape. Earlier emergence of flag leaves increases the number of septoria on upper leaves on any particular date, because there is more time for the fungus to develop and cause symptoms. When a breeding programme includes material with a wide range of maturity dates, selecting plants for resistance simply on the basis of septoria scores may be misleading because the plants with least septoria are likely to be the slowest to mature. A more effective approach is to regress disease scores on maturity dates. Plants with a large negative residual from the regression can be regarded as relatively resistant, allowing early maturity and septoria-resistance to be selected simultaneously [20].

**Induced resistance**

When a plant is attacked by a pest or a pathogen, it induces defences that involve the modification of cell walls, the killing of cells that contain or surround the pathogen and the induction of defence genes. It has long been known that the induction of such defences may be costly [2]. For example, in a pioneering experiment, barley that was heavily infected with an avirulent genotype of B. graminis f. sp. hordei had 7% lower grain yield, 4% smaller grains and 4% less protein per kg of grain than uninfected control plants [21]. Nevertheless, this early evidence for costs of induced resistance (IR) seems to have had remarkably little impact on thinking about disease resistance until quite recently [22••,23••]. The great majority of recent papers on costs of IR concern wild plants, a notable exception being that by Heil et al. [24] who showed that application of the defence elicitor benzo[1,2,3]thiadiazole (BTH) in the absence of fungal pathogens reduced plant biomass, the number of ears and the number of grains. These effects of BTH were most pronounced when nitrogen availability was limited. As the types of cost identified in reviews by Heil [22•] and by Heil and Baldwin [23••] are as relevant to crops as they are to wild plants or to model systems such as Arabidopsis, insights from research on wild and model plants should be broadly applicable to crops. This does not, however, negate the need for research on crops. For example, costs may be increased by stressful conditions, such as low soil fertility or the presence of competitors [22••,23••,24]. Experiments are needed to test the extent to which the burgeoning fundamental knowledge in this area is applicable to agriculture.

A particularly interesting class of IR-related costs concerns trade-offs between resistances to different types of pest or pathogen. There is now considerable evidence that resistance to certain pathogens induced by salicylic acid limits or even reduces the expression of resistance to other pathogens and pests induced by jasmonic acid or ethene, and vice versa. These trade-offs are reviewed by Felton and Korth [25].

**Gene-for-gene resistance**

The best-understood form of constitutive plant disease resistance is that following the GFG relationship. GFG resistances have been widely used in breeding, although they tend not to be durable because pathogens adapt to them rapidly by mutation of the avirulence (Avr) genes matching the R genes. New specificities of GFG R genes
are generated by variation in the number and sequence of leucine-rich repeats that they encode [26]. It is difficult to imagine how such polymorphism could involve costs of any significant kind, and the limited data available are consistent with this view. In tests of three sets of near-isogenic lines of barley, those with R genes against powdery mildew were compared to susceptible controls [5,8,9]. In two of these studies [5,8], the control was a single line, the recurrent susceptible parent, so comparisons of different lines with the control were confounded with each other. Nevertheless, no cost of R alleles was apparent in either of these studies [5,8]. In the third study [9], however, ten pairs of lines, either with a particular R gene or without it, were developed in cv. Manchuria. In pairwise comparisons, the R gene had no effect on grain yield, TGW or other agronomic characters. In a fourth experiment on barley powdery mildew, two R genes, Mla9 and Mla1, segregated in a doubled-haploid population. Once again, neither gene was associated with differences in grain yield or other yield components [27]. In a synthetic population of the outbreeding crop species rye, two GFG R genes that are effective against powdery mildew, Rm1 and rm2, segregated, although neither had a significant effect on fitness [28].

Nevertheless, gene expression data suggest that a cost may be associated with the number of GFG R genes that are involved in resistance to a particular pathogen. Overexpression of either Prf [29] or Pto [30] in tomato, which are both required for an effective response to the bacterium Pseudomonas syringae pv. tomato carrying the avrPto gene, causes constitutive activation of defence responses. A similar effect was produced by overexpression of RPS2, which is involved in resistance to Pseudomonas syringae in Arabidopsis [31]. Although overexpression of R genes leads to enhanced resistance to a wide range of pathogens [29,30], constitutive induction of defence genes is likely to be costly [22*,23**]. Consequently, if each GFG R gene independently induces a certain level of defence (which is yet to be tested when R genes are not overexpressed), there might be a marginal cost of each additional R gene. The number of such genes would be determined by a balance between that cost and the need to fight pathogens.

The R alleles that are observed in nature or in breeding material may be those that are associated with the lowest costs, such that other alleles have been eliminated by natural selection. Four mutant or recombinant alleles of the rp1 locus of maize, which controls GFG resistance to the rust Puccinia sorghi, confer necrotic phenotypes in the absence of the fungus [32]. If these lesion-mimic phenotypes reduce grain yield, as one would expect when green leaf area is reduced, these rp1 alleles would be replaced in natural populations by other genes that are similarly effective against rust but are less costly to the plant.

van der Biezen and Jones [33] proposed a new model of the function of GFG R genes that has a bearing on costs of resistance [34*]. The model, which has been developed by Dangl and Jones [35*], involves a tripartite interaction between a pathogen Avr factor (which is also involved in pathogenicity), a host pathogenicity target (PT; to which Avr binds) and the R protein (which binds to the PT–Avr complex and thereby induces an effective defence response). Such an interaction has been detected in Arabidopsis, in which the RIN4 protein binds to both RPM1, the product of a GFG R gene, and to two different Acr gene products that elicit resistance in RPM1 plants, AvrB and AvrRpm1 [36*]. The model postulates that R ‘guards’ PT by monitoring the binding of Avr but it relies on several hypotheses that have not yet been fully tested. For example, it hypothesises that Acr genes encode pathogenicity factors, although this has been demonstrated for only a small minority of the genes cloned to date [37*], and that mutations in Acr genes are costly in terms of pathogen fitness, even though less is known about virulence costs than about the costs of plant resistance. At the risk of piling hypothesis upon hypothesis, a further prediction is that PT proteins (as they are targets of pathogenicity [Avr] proteins) may have significant functions in plant defence or physiology (some data supporting this are given in [34*]). Consequently, a mutation in a PT gene that caused loss of binding of Avr to PT might be costly if it also caused loss of the normal activity of the PT protein. In contrast, a mutation in the leucine-rich repeat of the R protein that caused increased binding to the PT–Avr complex is unlikely to affect fitness, so providing the plant with low-cost surveillance for pathogens.

Partial resistance

An important goal of plant breeding is durable resistance that remains effective for a long time over a large area while being exposed to the pathogen. Resistance that is polygenic, race-non-specific and partial in its effect against the disease is often durable. In contrast, the monogenic, race-specific, complete resistance controlled by GFG relationships is often short lived. These are two extremes of many genetic models of resistance [38]. Nevertheless, Vanderplank [39] suggested that partial (i.e. ‘horizontal’) resistance (PR) may be eroded over many generations either if it is masked by effective GFG (i.e. ‘vertical’) resistance (the Vertifolia Effect) or if plants are not exposed to the disease [39], implying that PR is costly. Studies that lend some support to this idea include two presented by Vanderplank himself [39]: first, the apparent loss of PR to late blight (Phytophthora infestans) in the presence of effective GFG resistance in the breeding programme from which the potato cv. Vertifolia was produced, and second, the loss of PR to rust caused by Puccinia polysora in African and Asian landraces of maize. If PR does indeed incur a long-term cost, this should be of great concern to breeders because it implies that this useful form of durable resistance is liable to be lost if it is not actively and continuously selected. Nevertheless, Vanderplank’s hypothesis has not been critically tested and, in general, the relevant data could be interpreted in several ways. For example, was resistance lost in maize...
following its introduction into Africa and Asia or gained in American maize? It is true that it is more difficult to study many genes with small effects than one gene with a large effect, but this area of research surely deserves greater attention in the future.

A possible cost of PR may be inferred from data that suggest that one aspect of PR may be greater inducibility of defences in response to pathogen infection. Lines of tomato and cabbage with high resistance to *Alternaria solani* (early blight) and *Xanthomonas campestris* pv. *campestris*, respectively, accumulate higher levels of defence proteins faster than more susceptible lines [40]. In *Arabidopsis*, the *ISR1* locus controls both IR and basal resistance to *Pseudomonas syringae* pv. *tomato* [41]. Critical experiments that relate resistance, defence induction and costs have not yet been carried out, but it is possible that there may be a trade-off between high PR to disease and a high cost of inducing that resistance [22•, 23••].

**Case study: the *mlo* gene of barley**

The crop gene that has been most extensively studied from the point of view of yield and other costs is *mlo* in barley, which has provided excellent, durable resistance to powdery mildew and has been used widely in breeding, especially in Europe [42]. The wildtype allele, *Mlo*, is a negative regulator of defences against powdery mildew, including cell death, so loss of *Mlo* activity confers resistance to mildew and deregulated leaf cell death [43]. Since the early days of research on this gene, plants carrying the *mlo* mildew resistance allele have been found to suffer from spontaneous necrotic flecking, which is apparently not associated with mildew infection [6, 44].

*mlo* mildew resistance has long been associated with reduced grain yield [4–7]. In the most informative study of the association between *mlo* resistance and yield [6], doubled-haploid progeny of crosses between three *mlo* mutant lines and susceptible cultivars were grown in trials in which foliar diseases, including mildew, were controlled with fungicides. *mlo* (mildew-resistant) lines had an average yield that was 4.2% lower than that of *Mlo* (mildew-susceptible) lines. They also had 5.4% lower TGW and a much higher level of necrotic leaf spotting. It was concluded that the yield loss that was associated with *mlo* was probably caused by the spotting which, in turn, was a pleiotropic effect of *mlo*. It is unlikely that the yield reduction was caused by genes that are linked to *mlo* because similar costs were associated with three independent *mlo* mutations in different cultivars. Furthermore, necrotic spotting has been associated with every *mlo* allele tested [4–6]. By contrast, a quantitative trait locus (QTL) that decreased yield mapped close to but not at the *mlo11* gene in cv. Derkado [45, 46•]. In different analyses of the same data, grain number per stem [45] and TGW [46•] were identified as the main yield components affected. In both studies, however, more than one QTL controlling yield mapped to chromosome 4, on which *mlo* is located, which greatly increases the difficulty of mapping QTLs accurately [46•, 47]. The conclusion that yield reduction is a pleiotropic effect of *mlo* should therefore be regarded as sound [6]. As there is genetic variation in yield among the *mlo* lines of the various crosses studied [6, 7, 45, 46•], the detrimental effect of *mlo* mildew resistance on yield can be alleviated by recombining genes elsewhere in the genome by the normal process of plant breeding.

Another, superficially quite different, trade-off of *mlo* mildew resistance is that it increases the susceptibility of barley plants to facultative pathogens, including *Magnaporthe grisea*, which causes blast [48], and *Cochliobolus sativus*, which causes spot blotch [49•]. The initial, surprising discovery was that plants with *mlo* resistance to mildew were susceptible to blast. Specifically, they had massive growth of *M. grisea* in the mesophyll, large blast lesions and high levels of disease on the leaf. The increased susceptibility was consistent for three *mlo* alleles and so is probably a pleiotropic effect of *mlo*. *mlo* plants not only had higher levels of spot blotch caused by *C. sativus* but were also more susceptible to a culture filtrate containing a fungal toxin [49•]. This is consistent with the Mlo protein functioning partly as an antagonist of cell death, so that reduced Mlo activity leads both to spontaneous cell death, especially in the mesophyll, and to increased cell death when the plant is challenged by a toxin. Survival of host cells may restrict the growth of necrotrophic fungi, which are able to feed from dead cells. Indeed, in *Arabidopsis thaliana*, growth of *Botrytis cinerea* and *Sclerotia sclerotiorum* is promoted by the hypersensitive response [50]. There is evidently a trade-off between resistance to biotrophic fungi, such as *B. graminis*, which may involve death of host cells, and resistance to necrotrops, which is enhanced when host cells are kept alive.

Are trade-offs between *mlo* resistance to mildew and susceptibility to facultative fungi significant in agriculture? Spot blotch is a significant disease of barley in hotter climates [49•], where mildew is generally insignificant, whereas the main economic significance of blast is on rice rather than barley. *mlo* has been used most extensively in northern Europe, where mildew is important. Although the necrotic spotting associated with *mlo* may be linked to susceptibility to *C. sativus* [49•], there is no evidence as yet for a similar link with facultative diseases that are important in northern Europe, such as scald (*Rhynchosporium secalis*) or net blotch (*Drechslera teres*).

A third trade-off of *mlo* is in decreasing susceptibility to the arbuscular mycorrhizal fungus *Glomus mossae*, as measured by the amount of root cortex colonised and the abundance of mycorrhizal arbuscules [51]. As only one mutant allele, *mlo5*, was tested in this work, however, we cannot be certain that reduced mycorrhizal colonisation was caused by *mlo5* itself rather than by another gene. Clearly, the pleiotropic effects of *mlo* mean that the true value of this gene for plant breeding must be assessed in the context of...
the phenotype of the whole plant, including yield and yield components, as well as its responses to different kinds of microorganism.

Conclusions: putting it all together

A breeder must consider many factors when deciding whether or not to market a cultivar. By contrast, in the academic world, different people study agronomic properties and disease; and most often, different people study different diseases or at least different classes of disease. The lack of follow-up from key experiments done in the 1980s [6,10,21] has lead to a lack of integrated understanding of the effect of disease resistance on crop performance in the absence of disease. This may be substantially the result of this sub-division of research subjects. For example, if resistance is indeed costly, a breeder’s most effective strategy may not be to select for excellent resistance (if that means sacrificing yield or quality) but to select for at least moderate resistance while eliminating very susceptible lines, which might not only become heavily diseased themselves but also spread inoculum to other cultivars. The entire genotype of a cultivar rather than any single gene, no matter how important, determines its value to farmers and consumers, and therefore its commercial success or failure. It’s time to put the pieces back together for farmers and consumers, and therefore its commercial implications in breeding.

Acknowledgement

I would like to thank JDG Jones for helpful comments on the manuscript. The author’s work is supported by the Department of Agriculture, Environment and Rural Affairs for England.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


Despite the title, transgenic approaches to controlling wheat streak mosaic virus did not reduce disease symptoms. A non-transgenic R gene, Wsm1, was associated with a large yield penalty.


The authors describe an interesting exception to the tendency for introgression of wild grass DNA into wheat to cause a yield penalty. A translocation carrying a gene that confers resistance against barley yellow dwarf virus had no significant effect on wheat performance in the absence of disease.


A review of rapidly advancing research on the costs of induced resistance. This review discusses all forms of induced resistance, not just those triggered by jasmonate and ethene.


A second review on the costs of induced resistance. This review includes a particularly useful discussion of experimental approaches to investigating the effects of resistance on fitness and the mechanisms underlying fitness costs.


Biotic interactions


