OPINION

Science or alchemy?

Peter A. Lawrence

Hyperbole has become a common and accepted practice in science nowadays. We sell our results, we hide our ignorance and we use stock terms that gain spurious weight through repeated use. I illustrate from the field of developmental genetics.

> Words are … "innocent, neutral, precise, standing for this, describing that, meaning the other, so if you look after them you can build bridges across incomprehension and chaos. But when they get their corners knocked off they're no good anymore [...] I don't think writers are sacred but words are. They deserve respect. If you get the right ones in the right order, you can nudge the world a little or make a poem which children will speak for you when you're dead."
>
> Taken from The Real Thing by Tom Stoppard.

In science, as elsewhere, the ephemeral dictates of fashion determine how we write our reports. Just look at a journal in your field from only 20 years ago and marvel at how much the style of presentation and the use of English have changed (BOX 1). Jargon has always been there, but now it is increasingly laced with hype — the purpose being to persuade editors, other scientists and even ourselves that our results mean more than they do[1,2].

For example, take my field of developmental genetics, in which we now struggle to categorize each of tens of thousands of genes and assign them a function. You might have noticed that a particular thespian metaphor is at present being overused in most journals in this and related fields. For example, a typical paper might be entitled "A new player in the landing development pathway: The SKY domain of Plane1 plays a pilot's role in acting upstream of *Beacon5* to regulate *fuselage*". Does this metaphor help us to understand how proteins and genes interact to achieve 'landing'? Well it can, but it is becoming routine to use this figurative language to describe any developmental process, whether we understand its mechanism or not. We can use it to cover up ignorance, allowing the alchemy of spin to transform leaden pieces of information into fool's gold. Furthermore, by putting different findings into the same fancy dress, we disguise the distinction between trivial observation and illuminating discovery. The result can be a series of trite explanations that we will soon tire of.

The gene: a simple role

To illustrate my point, take a well-worked example of a biochemical pathway: 'the Wingless signalling pathway' (see link to Wnt gene homepage). In this pathway, a ligand (Wingless) binds to its transmembrane receptor (Frizzled) on the outer cell surface, from which the signal is transduced inside the cell and leads to biochemical changes to proteins (Dishevelled and Armadillo, for example) that affect gene transcription and cell behaviour[3]. There can be a single chain of events — a process that is 're-inacted' every time Wingless or another similar ligand is received by a cell. Further analysis of this pathway involves collecting mutations that alter cer-

Box 1 | Science in language: then and now

Here are two excerpts taken from papers published in 1977 and 2000, respectively. Both report on the same area of developmental biology: the function of *wingless* in *Drosophila melanogaster*. Note the growing use of acronyms in the more modern piece, which make the reading more cumbersome and obscure.

Then[11]:
"However, this is explicable if we assume that wingless is a member of a new class of homeotic mutations which affect cooperative decisions taken by [wing imaginal] discs as a whole rather than decisions taken individually by each cell. This interpretation is supported by the analysis of penetrance of *wingless*. We found that, unlike the other homeotic mutants mentioned above, the expression of *wingless* is all or none, so that, when expressed, all of the cells of the duplicated notum are transformed. We never find cases of partial transformation in which some cells are transformed into notum and others remain wing. Since the probability of one disc being transformed does not affect the probability of any of the others, the decision whether to differentiate a normal wing or a duplicated notum is taken by each disc independently. Thus, it seems that the *wingless* mutation is a defect in a decision made by groups of cells."

Now[12]:
Expression of *dpp* in the VM responds to Wg signalling. We show that *wg* and *dTcf* mutations eliminate BE reporter gene expression in PS3 and slightly reduce it in PS7. A similar result was reported for Dpp protein in an *arm* mutant background. Our result is surprising because *Drosophila* embryos have a large amount of maternal embryonic *dTcf* RNA. We were not expecting the null *dTcf* phenotype to be similar to that of *wg*, which is expressed only zygotically. We conclude that Wg signalling is required for activation of *dpp* in PS3 and assists in the activation in PS7. We also suggest that the maternal contribution of dTcf may not play a role in this activation."

tain aspects of the signalling cascade, such as mutations that affect proteins that are needed to process the ligand or transmit the signal to the nucleus. After the proteins have been identified, their function can, in principle and sometimes in practice, be determined by direct biochemical experiments. For example, we can find out whether the products of two genetically interacting loci also physically bind to each other or whether a protein has any recognizable enzymatic activity. If, in the absence of a gene product, the process is affected in some way, the conclusion is reached that the gene is a 'player' in the pathway. The next step, certainly for those of us who work on fruitflies, is the cute naming of the gene, a name often chosen to make it stick in the mind, and — there is a further motive — to launch the scientist's career, hopefully like a rocket in the first phase of its trajectory.

The gene: an impossible role

This approach has proved to be powerful and effective, mainly because the process is a biochemical pathway in which proteins function in a standard sequence. But problems arise when this same pathway logic is extended, as it frequently is, to describe the process of building an embryo or an organ. This process is dubbed a developmental pathway. By looking at a recent issue of a primary journal, I found that, out of 18 papers, 11 were developmental pathway papers and, of these, 8 had the word 'role' in the abstract or title. In this kind of analysis, we might not have a biochemical pathway, but the same logic is forced to fit: in this case, mutations are collected that affect not a particular signal-transduction pathway but something rather grand, such as the making of a wing. Take *wingless* again: long ago we started with *wingless-1* — a *Drosophila* mutation with a clear-cut but ultimately misleading phenotype. The homozygous mutant flies often lacked one or both wings, which were replaced by an extra bit of thorax[4]. Over the years we concluded from the study of *wingless-1* that the *wingless* gene 'played a role' in cooperation between cells, in preventing cell death, in sponsoring cell death, in promoting growth and in determining cell identity. Much effort was then expended, and many papers were written, in trying to work out when and where the *wingless* gene was needed. But these studies often made the explicit or implicit assumption that the gene belonged to a standard pathway and that it was therefore needed only at one time and/or in one place during development. It was later found that *wingless-1*, which had been studied for some years, was actually only the result of a slight, localized reduction-in-function of the gene[5]. Loss-of-function mutations in *wingless* had a much more devastating effect on development, with the embryos dying early because of numerous and catastrophic failures in many processes, including segmentation[6]. Further studies showed that, indeed, the *Wnt* class of gene, of which *wingless* is the archetypal member, encodes proteins that are used at many times and in many places during the development of worms, flies and vertebrates, affecting countless events directly and indirectly. But the one-time-and-place assumption still lurks behind the analyses of many developmental pathways, and I suspect that for most genes it will prove to be false.

"I'd like a style without the substance."

Figure 1 | Courtesy of CartoonStock

"Modern scientists, competing for recognition and support, would prefer not to admit that they might be studying a boring or trivial gene, so the 'role' of the gene in question has to be dressed up with an impressive adjective."

It is probable that a large fraction of the fruitfly genome is needed to build a wing, but each gene that is defined as instrumental in some way by pathway experiments is usually awarded a 'major role'. Modern scientists, competing for recognition and support, would prefer not to admit that they might be studying a boring or a trivial gene, so the 'role' of the gene in question has to be dressed up with an impressive adjective (FIG. 1). What follows are examples of such adjectives that I found in a quick sweep of recent papers: major, pivotal, key, global, potent, leading, important, principal, vital, critical, regulatory, endogenous, master, multiple, controlling, fundamental, special, dual, basic, specific, essential, novel, evolving, potential, new, changing, active, central, functional, counteractive, prominent, very specific, very important and essential, legitimate, biological, physiological, integral, more important role than previously suspected.

This enjoyable list tells us only that the scientist is trying to boost his or her gene.

Always the leading part?

What makes us think our gene is needed for a developmental process? What we mean in almost every case is that, in the absence of the gene or its product, the process under study goes awry. Of course, this is the principle on which genetic experiments have always been interpreted, and it is a perfectly acceptable one. The problem comes when we try to rank the importance of the gene itself. I do not think it is correct to conclude that the gene must be a major or pivotal one if the process does not work in its absence. I think that here the logic breaks down, both in biology and certainly in drama — the source of this role model. Consider *Romeo and Juliet*[7] (also see link to the web's first edition of the Complete Works of William Shakespeare) (BOX 2). For the play to work, we obviously need the star-crossed lovers as well as some other characters. But do they all play major roles? What about Friar Laurence who, in trying to help the lovers, unwittingly engineers the tragedy? His role is clearly a major one because he speaks so many lines of importance to the substance and meaning of the play itself. But do you think Friar John plays a leading role in the play? Friar John only has a few lines, but is entrusted by Friar Laurence with the delivery of a vital letter. He fails to do so because, off stage, he is locked into a house with the letter. The result is that Romeo is not informed about the sleeping draft and he fatally assumes that his beloved Juliet, immobile in the tomb, is dead. So if Friar John and his failure were removed from the plot the play would break down completely; nevertheless, try using that argument to persuade a leading actor to take his part! Then there is the apothecary, who has very few lines — again the plot needs him or at least his mortal drug. The truth is that, because the drama has few, if any, dispensable char-

Box 2 | Changing perceived identity: Romeo and Juliet

Scene from the recent production of William Shakespeare's *Romeo and Juliet* by the Royal Shakespeare Company. This famous passage from the balcony scene emphasizes the use of words (in this case names) in changing perceived identity.

JULIET
"Tis but thy name that is my enemy; . . ."

ROMEO
"I take thee at thy word:
Call me but love, and I'll be new baptized;
Henceforth I never will be Romeo."

Image courtesy of EPO Online © (2000) Royal Shakespeare Company. Photo by Robert Workman.

acters, a geneticist might well conclude that they all play leading roles. This is not a discriminatory conclusion and is therefore not useful. If you allow this logic, and my claim that a large portion of the genome is needed to build a wing, the end result could be thousands of papers, each concluding in the most tedious of ways that the gene studied plays a major role in wing-building. Indeed, I think we have gone a little way down that road already. Why do we do it? Maybe because when we award a gene a 'major' role we aim to make a virtue of our ignorance of the function of the protein.

Fashionable genes

Can we rank the importance of genes in development? Yes, but only if we can agree on criteria, and that might not be possible. I would think that, for a developmental biologist, a gene needed for the determination of cell fate (such as a homeotic gene in the Bithorax Complex) is more important than one needed for the integrity of each cell (such as tubulin). But for a cell biologist the opposite would be true. Ranking is also dependent on fashion: when gene cloning first became possible, the presence of a zinc finger or a homeobox gave the gene star quality, but once these genes became too abundant they lost their cachet. To catch the eye, it became better to have a gene that encoded an integral membrane protein, but they too later slipped from top billing. Now secreted proteins are the stars, whether they deserve it (whether they — another magic word — 'signal') or not.

Talent spotting

Another problem is that new genes that belong to developmental pathways may be searched for (necessarily) in artificial conditions, when the developmental system is seriously weakened by a secondary mutation — rather like using impaired gait to find and study chilblains in a person with gout. This method might be useful to find many genes that have no mutant phenotype on their own. But the importance of such genes to the process under study is hard to gauge; a nice example is given in *Drosophila* by the frizzled genes, which encode Wingless receptors. There are at least two of these receptors (*frizzled* and *frizzled-2*) — remove either and the flies seem as good as wild type. One might conclude from this that each frizzled gene is unimportant. But remove both and the flies die as embryos because their Wingless reception is blocked[8], and the conclusion is immediately drawn that the two genes do something 'major' together. However, the *Drosophila* genome sequence has revealed more frizzled receptors[9]. If these have survived in the fly genome unscathed by stop codons, presumably they do something. Does their apparent obscurity make them 'minor'? Maybe, maybe not; we just do not know yet. Better not to talk up our gene now; better to let the facts do the talking for us when we find them.

So why do we hype our results? The short answer is that everybody else is doing it and we fear that unless we hype our findings as well we will not have access to those few all-important top journals. The solution is to change the climate to reduce the pressure on everyone to publish in the same few journals[10]. We scientists could, for example, try to remember that the real value of a piece of work resides not in where it was published, but in whether it is right, how much it illuminates, where any new understanding leads to and how long it has proved or will prove relevant and useful. We could try to raise our consciousness about this and move away from journal-based assessment, which often occurs when we compare scientists for promotion or when we evaluate job or grant applicants. At that time, which might be years after the publication of the papers, we have a big advantage over the editors and their reviewers who then had to decide whether to publish or not: we have hindsight — and we should use it.

It is time we scientists stopped overselling ourselves, our results or our institutions. It is not scientific to do so. It is also unwise because we will regret it when those who fund us find us out. We should realize that spin doctoring and science are as mutually supportive as cats and dogs.

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Links

DATABASE LINKS *wingless-1* | *thorax* | *frizzled* | *frizzled-2* | Bithorax complex
FURTHER INFORMATION Lawrence lab homepage | The *Making of a Fly* | Roel Nusse's Wnt gene homepage | *The Real Thing* | The web's first edition of the Complete Works of William Shakespeare | Royal Shakespeare Company | EPO online

1. Rosner, J. L. Reflections of science as a product. *Nature* **345**, 108 (1990).
2. Martin, R. G. Scientific hype. *The New Biologist* **2**, 747–749 (1990).
3. Wodarz, A. & Nusse, R. Mechanisms of Wnt signalling in Development. *Annu. Rev. Cell Dev. Biol.* **14**, 59–88 (1998).

4. Sharma, R. P. & Chopra, V. L. Effect of *wingless* (*wg*) mutation on wing and haltere development in *Drosophila melanogaster*. *Dev. Biol.* **48**, 461–465 (1976).
5. Baker, N. E. Molecular cloning of sequences from wingless, a segment polarity gene in *Drosophila*: the spatial distribution of a transcript in embryos. *EMBO J.* **6**, 1765–1774 (1987).
6. Nusslein-Volhard, C., Wieschaus, E. & Kluding, H. Mutations affecting the pattern of the larval cuticle in *Drosophila melanogaster*. *Roux Arch. Dev. Biol.* **193**, 267–282 (1984).
7. *The Complete Works of Shakespeare* 4th edn (ed. Bevington, D.) (Harlow Longman, New York, 1997).
8. Chen, C. M. & Struhl, G. Wingless transduction by the Frizzled and Frizzled2 proteins of *Drosophila*. *Development* **126**, 5441–5452 (1999).
9. Adams, M. D. *et al.* The genome sequence of *Drosophila melanogaster*. *Science* **287**, 2185–2195 (2000).
10. Editorial. Citation data: the wrong impact? *Nature Neurosci.* **1**, 641–642 (1998).
11. Morata, G. & Lawrence, P. The development of wingless, a homeotic mutation of *Drosophila*. *Dev. Biol.* **56**, 227–240 (1977).
12. Yang, X. *et al. decapentaplegic* is a direct target of dTcf repression in the *Drosophila* visceral mesoderm. *Development* **127**, 3695–3702 (2000).

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OPINION

At the interfaces of epidemiology, genetics and genomics

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You come onto the court prepared for tennis but your partner seems to be ready for rugby. Neither of you is at all sure what it is that your opponent wants to play. The only recourse is to teach each other the rules of your own game and then decide whether you can collectively invent a new sport. Welcome to the dialogue at the intersections of epidemiology with genetics and genomics.

Epidemiology is the population-based study of disease patterns and their determinants. It is mostly an observational science (like astronomy, palaeontology and evolutionary biology), and so is distinguishable from experimental sciences; it involves the study of people with and without disease (unlike most clinical research); and the primary measures of comparison involve calculations of risks (probability of disease given exposure) and rates (frequency of disease per unit of population per unit time). The most common of these measures is the rate (or risk) ratio (also called the relative risk) — the rate of disease in the exposed (the numerator) divided by the rate of disease in the unexposed (the denominator).

Because epidemiology is an observational science, those being studied are not allocated to exposed and unexposed conditions by the researcher. So, other characteristics can correlate with the exposure of interest by chance or by choice. Furthermore, because free-living people make choices about participating in studies, the groups being studied (exposed versus unexposed; those with and without disease) might or might not be comparable with the population about whom inferences are made; that is, there might be bias. These problems are not insurmountable but require careful attention to study design and analysis; their solutions are central to good epidemiological practice.

Originally focused on infectious disease, epidemiology began as a discipline that used both laboratory and field methods. Its procedures involved, on the one hand, recruiting both the affected and unaffected to determine the disease vector and time and place of exposure, and, on the other, characterizing the biology of the microorganisms and the disease. As epidemiological methods were increasingly applied to chronic conditions, relevant, measurable intermediate biology (for example, the association between high serum lipids and coronary heart disease) ensured that this integration of field and laboratory methods could be adopted for cardiovascular epidemiology.

Cancer epidemiology was less able to take this road for several reasons: cancer was clearly a multiplicity of rarer diseases; there were no widely applicable intermediate markers; and initial studies of lung cancer identified a self-reported exposure — smoking — that was associated with a large relative risk[1], encouraging the belief that identifying the causes of cancer would not be difficult. The fact that high-dose radiation also increased the risk of developing cancer reinforced this perspective. This hope has subsequently proved illusory for many cancers.

With the increasing understanding that cancer arises from multiple genetic and epigenetic alterations, and with the development of high-throughput techniques that rapidly characterize biological material, we have entered an era when susceptibility, intermediate processes and subsets of cancers themselves can be defined molecularly in large numbers. Accordingly, fields of science that developed independently — epidemiology, genetics and molecular biology — find themselves with overlapping interests, but with differences in study designs, techniques, emphases and dialects. A proper understanding of language and study-design issues is essential to the melding of these fields. This crosstalk, perhaps at present most vigorous in cancer research, also has implications for understanding the aetiology of other diseases, such as diabetes, allergic disorders and neurodegenerative disease.

There have been several papers on related issues, including methods for genetic epidemiology[2] and whether medicine should be 'clothed in a genetic mantle'[3]. By contrast, I would like to approach this topic from five directions — language and concepts; observational versus experimental study designs; taxonomies of cancer-associated alleles; the use of numerators and denominators; and the genetics of susceptibility and protection. My general position is that these are some of the issues that need to be aired, if not resolved, to facilitate communication across the boundaries of these fields.

Language and concepts

Given the markedly different training of epidemiologists and geneticists, it is not surprising that different terms exist for the same concepts. For instance, 'association studies' (genetics) and 'case–control studies' (epidemiology) embody the same design concepts — people with and without the phenotype of interest are compared on the basis of their exposure (epidemiology) or genotype (both genetics and epidemiology).

Conversely, there are some concepts that are poorly understood and the associated terms tend to be misused, in both discussion and print. For instance, in epidemiology, 'confounding' has a specific meaning with both conceptual and mathematical definitions. As a concept born out of the nature of observational science, it addresses a problem inherent in seeking causal interpretations: that of mistaking potential causes with factors that are associated both with a real causal factor and the disease itself. The most obvious example of a confounder is age: an association might be found between age and cancer simply because the patterns of exposure in a population have changed over time or because older people have been exposed for longer.