George et al. (page 975) identify one of the same four germline mutations in 2 of 96 patients with apparently sporadic neuroblastoma (as other members of the families to which these two individuals belonged were not examined). Moreover, these studies report that 59 of 617 (9.6%) sporadic neuroblastoma cases they investigated have somatic single-nucleotide mutations in ALK. Such somatic mutations were associated with more aggressive tumours and lethal cases of this cancer.

These studies also found that, in contrast to normal ALK, the mutated enzyme was variably phosphorylated and had increased kinase activity in a mutation-specific way. Similarly, downstream targets of ALK were activated by the mutations in this enzyme in a mutation-dependent manner. Could the increased activity of ALK in neuroblastoma be inhibited for treatment purposes? For example, a leucine for arginine substitution at position 1275 was associated with phosphorylation of AKT and AKT proteins, whereas the replacement of arginine by glutamine at position 1275 was associated with phosphorylation of AKT and the ERK1/2 protein. Although these data hint that ALK inhibition could be a viable strategy for the treatment or prevention of neuroblastoma, they also indicate that multi-agent targeted therapy as well as nonspecific kinase inhibitors make sense, given that multiple signalling pathways consisting of several kinases are involved.

Mossé et al. and Janoueix-Lerosey et al. find that although members of 6 of the 16 families they examined do not harbour mutations in ALK and PHOX2B, neuroblastoma runs in these pedigrees. At least three possibilities, which are not mutually exclusive, could explain these observations. First, mutations in other genes, such as MYCN, might be involved. Second, because ALK-mediated neuroblastoma involves increased activity of this protein, germline mutations in promoter sequences that favour ALK expression are possible. Third, large genomic deletions and rearrangements could occur in the germ line. Somatic translocations involving ALK have been reported, and so germline rearrangements in the sequence of this gene are also plausible. ALK deletions associated with neuroblastoma seem counter-intuitive, however, because it is increased ALK activity — rather than its absence — that seem to lead to this cancer. But germline deletions in regions containing repressors of ALK expression, as well as partial deletions creating ALK-like proteins, new proteins distinct from ALK, or continuously active kinases, are among plausible mechanisms.

Chen et al. and Mossé and colleagues provide evidence that somatic ALK mutations associate with aggressive forms of neuroblastoma in sporadic cases. Several questions arise from these observations. For example, will somatic mutations make ALK-associated familial neuroblastoma more aggressive? If the answer is yes, should adjuvant therapy — perhaps ALK inhibitors — accompany surgical removal of the tumour? Could it be that ALK inhibition is toxic rather than beneficial in cancer cases caused by germline mutations? After all, every single cell in the body will carry the mutation, albeit with differential expression in different tissues.

The past two years have seen an explosion in genome-wide association studies, which have shown that variations of certain genes with low penetrance account for a small subset of various common cancers. At present, these data are not associated with much clinical context, and so cannot meaningfully contribute to genetic counselling and cancer management. In this era of genomic medicine, the long-awaited discovery of a major non-syndromic neuroblastoma gene is indeed a welcome advance for taking pre-emptive measures (Box 1). ■

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PHILOSOPHY OF SCIENCE

Theories of almost everything

P.-M. Binder

A provocative contribution to the logic of science extends the theorems of Kurt Gödel and Alan Turing, and bears on thinking about prediction, the standard model of particles, and quantum gravity.

Since 1620, when Francis Bacon’s Novum Organum set out the basic guidelines, the task of science has been to condense multiple observations into brief, general descriptions of natural phenomena. This process, called induction, helps us understand and predict the world around us. Enquiries into the limits of science have involved asking questions such as “Can we know everything about the natural world?”, which have so far gone unanswered. Writing in Physica D, David Wolpert has made headway in this direction by demonstrating that the entire physical Universe cannot be fully understood by any single inference system that exists within it.

Various major scientific developments of the twentieth century have placed limits on different facets of knowledge. These include the measurement process (quantum mechanics, through Heisenberg’s uncertainty principle); the transmission of information (relativity, through the constancy of the speed of light); the ability to predict the future from less-than-perfect measurements in the present (chaos theory, through sensitive dependence on initial conditions); and the efficient prediction of certain natural phenomena before they unfold (complex systems theory, through intractability).

Wolpert’s work follows another path, that of Kurt Gödel and Alan Turing’s theorems of incompleteness developed in mathematics and computation (Box 1), and he extends them to address the logic of science. He introduces the idea of inference machines — physical devices that may or may not involve human input — that can measure data and perform computations, and that model how we come to understand and predict nature. He develops a formal description of all such inference machines in terms of two functions: one stipulates the initial state of a machine (the set-up function) and the other (the conclusion function) describes the observations, recollections or predictions it makes — in other words, a ‘theory’.

In proving his theorems, Wolpert defines U as the space of all world-lines (sequences of events) in the Universe that are consistent with the laws of physics. He then defines strong inference as the ability of one machine to predict the total conclusion function of another machine for all possible set-ups. Finally, he uses ‘Cantor diagonalization’ (Box 1) to prove, among others, the following two statements:

(1) Let C be any strong inference machine for U. There is another machine, C₂, that cannot be strongly inferred by C₁.
(2) No two strong inference machines can be strongly inferred from each other.

The first of these statements posits that there is a portion of ‘knowledge space’ (that inferable by C₂) that is not available to any C₁ machine. The second is a statement about the non-equivalence of inference machines; it implies that, at most, only one machine at one
In 1874, Georg Cantor published a proof of the existence of uncountable infinities. He started by labelling points in the interval \([0, 1]\) with the countable infinite natural numbers \((1, 2, 3, \ldots)\) as follows:

\[
a_1 = 0.d_{11}d_{12}d_{13}d_{14}\ldots
\]

\[
a_2 = 0.d_{21}d_{22}d_{23}d_{24}\ldots
\]

\[
a_3 = 0.d_{31}d_{32}d_{33}d_{34}\ldots
\]

\[
\vdots
\]

All \(d\)s are digits between 0 and 9. There is at least one number \(a = 0.d_{11}d_{12}d_{13}\ldots\) in the unit interval \([0, 1]\) such that \(d_1 \neq d_{11}, d_2 \neq d_{22}, \ldots\) and so on, guaranteeing that it differs from each number in the list by at least one digit, and hence it cannot be in the list. This proves that the number of points in the unit interval is not countable, a proof known as Cantor diagonalization. A related result, the diagonal lemma, has played an important part in the proof of several incompleteness theorems. In 1931, Kurt Gödel proved that any mathematical system that includes enough of the theory of natural numbers contains statements that cannot be proved to be either true or false, and is thus incomplete. The general argument for the proof is based on Epimenides' liar's paradox — is 'This sentence is false' a true or a false statement? — but it replaces 'false' with 'unprovable'. The construction of a number that represents a concrete, undecidable statement requires diagonalization techniques.

In the mid-1930s, Alan Turing used similar methods to prove that no general algorithm can determine whether a given Turing machine — a computer — halts for a given input. It is thus not surprising that Wolpert's proofs also rely on diagonalization arguments.

P.-M.B.