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Strong Inference

Certain systematic methods of scientific thinking may produce much more rapid progress than others.

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Scientists these days tend to keep up a polite fiction that all science is equal. Except for the work of the misguided opponent whose arguments we happen to be refuting at the time, we speak as though every scientist's field and methods of study are as good as every other scientist's, and perhaps a little better. This keeps us all cordial when it comes to recommending each other for government grants.

But I think anyone who looks at the matter closely will agree that some fields of science are moving forward very much faster than others, perhaps by an order of magnitude, if numbers could be put on such estimates. The discoveries leap from the headlines—and they are real advances in complex and difficult subjects, like molecular biology and high-energy physics. As Alvin Weinberg says (*1*), "Hardly a month goes by without a stunning success in molecular biology being reported in the Proceedings of the National Academy of Sciences."

Why should there be such rapid advances in some fields and not in others? I think the usual explanations that we tend to think of—such as the tractability of the subject, or the quality or education of the men drawn into it, or the size of research contracts—are important but inadequate. I have begun to believe that the primary factor in scientific advance is an intellectual one. These rapidly moving fields are fields where a particular method of doing scientific research is systematically used and taught, an accumulative method of inductive inference that is so effective that I think it should be given the name of "strong inference." I believe it is important to examine this method, its use and history and rationale, and to see whether other groups and individuals might learn to adopt it profitably in their own scientific and intellectual work.

In its separate elements, strong inference is just the simple and old-fashioned method of inductive inference that goes back to Francis Bacon. The steps are familiar to every college student and are practiced, off and on, by every scientist. The difference comes in their systematic application. Strong inference consists of applying the following steps to every problem in science, formally and explicitly and regularly:

1) Devising alternative hypotheses;

2) Devising a crucial experiment (or several of them), with alternative possible outcomes, each of which will, as nearly as possible, exclude one or more of the hypotheses;

3) Carrying out the experiment so as to get a clean result;

1′) Recycling the procedure, making subhypotheses or sequential hypotheses to refine the possibilities that remain; and so on.

It is like climbing a tree. At the first fork, we choose—or, in this case, "nature" or the experimental outcome chooses—to go to the right branch or the left; at the next fork, to go left or right; and so on. There are similar branch points in a "conditional computer program," where the next move depends on the result of the last calculation. And there is a "conditional inductive tree" or "logical tree" of this kind written out in detail in many first-year chemistry books, in the table of steps for qualitative analysis of an unknown sample, where the student is led through a real problem of consecutive inference: Add reagent A; if you get a red precipitate, it is subgroup alpha and you filter and add reagent B; if not, you add the other reagent, B′; and so on.

On any new problem, of course, inductive inference is not as simple and certain as deduction, because it involves reaching out into the unknown. Steps 1 and 2 require intellectual inventions, which must be cleverly chosen so that hypothesis, experiment, outcome, and exclusion will be related in a rigorous syllogism; and the question of how to generate such inventions is one which has been extensively discussed elsewhere (*2, 3*). What the formal schema reminds us to do is to try to make these inventions, to take the next step, to proceed to the next fork, without dawdling or getting tied up in irrelevancies.

It is clear why this makes for rapid and powerful progress. For exploring the unknown, there is no faster method: this is the minimum sequence of steps. Any conclusion that is not an exclusion is insecure and must be rechecked. Any delay in recycling to the next set of hypotheses is only a delay. Strong inference, and the logical tree it generates, are to inductive reasoning what the syllogism is to deductive reasoning, in that it offers a regular method for reaching firm inductive conclusions one after the other as rapidly as possible.

"But what is so novel about this?" someone will say. This is *the* method of science and always has been; why give it a special name? The reason is that many of us have almost forgotten

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it. Science is now an everyday business. Equipment, calculations, lectures become ends in themselves. How many of us write down our alternatives and crucial experiments every day, focusing on the *exclusion* of a hypothesis? We may write our scientific papers so that it looks as if we had steps 1, 2, and 3 in mind all along. But in between, we do busywork. We become "method-oriented" rather than "problem-oriented." We say we prefer to "feel our way" toward generalizations. We fail to teach our students how to sharpen up their inductive inferences. And we do not realize the added · that the regular and explicit of alternative hypotheses and sharp exclusions could give us at every step of our research.

The difference between the average scientist's informal methods and the methods of the strong-inference users is somewhat like the difference between a gasoline engine that fires occasionally and one that fires in steady sequence. If our motorboat engines were as erratic as our deliberate intellectual efforts, most of us would not get home for supper.

Molecular Biology

The new molecular biology is a field where I think this systematic method of inference has become widespread and effective. It is a complex field; yet a succession of crucial experiments over the past decade has given us a surprisingly detailed understanding of hereditary mechanisms and the control of enzyme formation and protein synthesis.

The logical structure shows in every experiment. In 1953 James Watson and Francis Crick proposed that the DNA molecule—the "hereditary substance" in a cell—is a long two-stranded helical molecule (*4*). This suggested a number of alternatives for crucial test. Do the two strands of the helix stay together when a cell divides, or do they separate? Matthew Meselson and Franklin Stahl used an ingenious isotope-density-labeling technique which showed that they separate (*5*). Does the DNA helix always have two strands, or can it have three, as atomic models suggest? Alexander Rich showed it can have either, depending on the ionic concentration (*6*). These are the kinds of experiments John Dalton would have liked, where the combining entities are not atoms but long macromolecular strands.

Or take a different sort of question: Is the "genetic map"—showing the statistical relationship of different genetic characteristics in recombination experiments—a one-dimensional map like the DNA molecule (that is, a linear map), as T. H. Morgan proposed in 1911, or does it have two-dimensional loops or branches? Seymour Benzer showed that his hundreds of fine microgenetic experiments on bacteria would fit only the mathematical matrix for the one-dimensional case (*7*).

But of course, selected crucial experiments of this kind can be found in every field. The real difference in molecular biology is that formal inductive inference is so systematically practiced and taught. On any given morning at the Laboratory of Molecular Biology in Cambridge, England, the blackboards of Francis Crick or Sidney Brenner will commonly be found covered with logical trees. On the top line will be the hot new result just up from the laboratory or just in by letter or rumor. On the next line will be two or three alternative explanations, or a little list of "What he did wrong." Underneath will be a series of suggested experiments or controls that can reduce the number of possibilities. And so on. The tree grows during the day as one man or another comes in and argues about why one of the experiments wouldn't work, or how it should be changed.

The strong-inference attitude is evident just in the style and language in which the papers are written. For example, in analyzing theories of antibody formation, Joshua Lederberg (*8*) gives a list of nine propositions "subject to denial," discussing which ones would be "most vulnerable to experimental test."

The papers of the French leaders François Jacob and Jacques Monod are also celebrated for their high "logical density," with paragraph after paragraph of linked "inductive syllogisms." But the style is widespread. Start with the first paper in the *Journal of Molecular Biology* for 1964 (*9*), and you immediately find: "Our conclusions . . . might be invalid if . . . (i) . . . (ii) . . . or (iii). . . . We shall describe experiments which eliminate these alternatives." The average physicist or chemist or scientist in any field accustomed to less closely reasoned articles and less sharply stated inferences will find it a salutary experience to dip into that journal almost at random.

Resistance to Analytical Methodology

This analytical approach to biology has sometimes become almost a crusade, because it arouses so much resistance in many scientists who have grown up in a more relaxed and diffuse tradition. At the 1958 Conference on Biophysics, at Boulder, there was a dramatic confrontation between the two points of view. Leo Szilard said: "The problems of how enzymes are induced, of how proteins are synthesized, of how antibodies are formed, are closer to solution than is generally believed. If you do stupid experiments, and finish one a year, it can take 50 years. But if you stop doing experiments for a little while and *think* how proteins can possibly be synthesized, there are only about 5 different ways, not 50! And it will take only a few experiments to distinguish these."

One of the young men added: "It is essentially the old question: How *small* and *elegant* an experiment can you perform?"

These comments upset a number of those present. An electron microscopist said, "Gentlemen, this is off the track. This is philosophy of science."

Szilard retorted, "I was not quarreling with third-rate scientists: I was quarreling with first-rate scientists."

A physical chemist hurriedly asked, "Are we going to take the official photograph before lunch or after lunch?"

But this did not deflect the dispute. A distinguished cell biologist rose and said, "No two cells give the same properties. Biology is the science of heterogeneous systems." And he added privately, "You know there are *scientists*; and there are people in science who are just working with these oversimplified model systems—DNA chains and in vitro systems—who are not doing science at all. We need their auxiliary work: they build apparatus, they make minor studies, but they are not scientists."

To which Cy Levinthal replied: "Well, there are two kinds of biologists, those who are looking to se if there is one thing that can be understood, and those who keep saying it is very complicated and that nothing can be understood. . . . You must study the *simplest* system you think has the properties you are interested in."

As they were leaving the meeting, one man could be heard muttering, "What does Szilard expect me to do—shoot myself?"

Any criticism or challenge to consider changing our methods strikes of course at all our ego-defenses. But in this case the analytical method offers the possibility of such great increases in effectiveness that it is unfortunate that it cannot be regarded more often as a challenge to learning rather than as a challenge to combat. Many of the recent triumphs in molecular biology have in fact been achieved on just such "oversimplified model systems," very much along the analytical lines laid down in the 1958 discussion. They have not fallen to the kind of men who justify themselves by saying, "No two cells are alike," regardless of how true that may ultimately be. The triumphs are in fact triumphs of a new way of thinking.

High-Energy Physics

This analytical thinking is rare, but it is by no means restricted to the new biology. High-energy physics is another field where the logic of exclusions is obvious, even in the newspaper accounts. For example, in the famous discovery of C. N. Yang and T. D. Lee, the question that was asked was: Do the fundamental particles conserve mirror-symmetry or "parity" in certain reactions, or do they not? The crucial experiments were suggested: within a few months they were done, and conservation of parity was found to be excluded. Richard Garwin, Leon Lederman, and Marcel Weinrich did one of the crucial experiments. It was thought of one evening at suppertime: by midnight they had rearranged the apparatus for it: and by 4 a.m. they had picked up the predicted pulses showing the nonconservation of parity *(10)*. The phenomena had just been waiting, so to speak, for the explicit formulation of the alternative hypotheses.

The theorists in this field take pride in trying to predict new properties or new particles explicitly enough so that if they are not found the theories will fall. As the biologist W. A. H. Rushton has said *(11)*, "A theory which cannot be mortally endangered cannot be alive." Murray Gell-Mann and Yuval Ne'eman recently used the particle grouping which they call "The Eightfold Way" to predict a missing particle, the Omega-Minus, which was then looked for and found *(12)*. But one alternative branch of the theory would predict a particle with one-third the usual electronic charge, and it was not found in the experiments, so this branch must be rejected.

The logical tree is so much a part of high-energy physics that some stages of it are commonly built, in fact, into the electronic coincidence circuits that detect the particles and trigger the bubble-chamber photographs. Each kind of particle should give a different kind of pattern in the electronic counters, and the circuits can be set to exclude or include whatever types of events are desired. If the distinguishing criteria are sequential, they may even run through a complete logical tree in a microsecond or so. This electronic preliminary analysis, like human preliminary analysis of alternative outcomes, speeds up progress by sharpening the criteria. It eliminates hundreds of thousands of the irrelevant pictures that formerly had to be scanned, and when it is carried to its limit, a few output pulses, hours apart, may be enough to signal the existence of the antiproton or the fall of a theory.

I think the emphasis on strong inference in the two fields I have mentioned has been partly the result of personal leadership, such as that of the classical geneticists in molecular biology, or of Szilard with his "Midwest Chowder and Bacteria Society" at Chicago in 1948–50, or of Max Delbrück with his summer courses in phage genetics at Cold Spring Harbor. But it is also partly due to the nature of the fields themselves. Biology, with its vast informational detail and complexity, is a "high-information" field, where years and decades can easily be wasted on the usual type of "low-information" observations or experiments if one does not think carefully in advance about what the most important and conclusive experiments would be. And in high-energy physics, both the "information flux" of particles from the new accelerators and the million-dollar costs of operation have forced a similar analytical approach. It pays to have a top-notch group debate every experiment ahead of time: and the habit spreads throughout the field.

Induction and Multiple Hypotheses

Historically, I think, there have been two main contributions to the development of a satisfactory strong-inference method. The first is that of Francis Bacon *(13)*. He wanted a "surer method" of "finding out nature" than either the logic-chopping or all-inclusive theories of the time or the laudable but crude attempts to make inductions "by simple enumeration." He did not merely urge experiments, as some suppose: he showed the fruitfulness of interconnecting theory and experiment so that the one checked the other. Of the many inductive procedures he suggested, the most important, I think, was the conditional inductive tree, which proceeded from alternative hypotheses (possible "causes," as he calls them), through crucial experiments ("Instances of the Fingerpost"), to exclusion of some alternatives and adoption of what is left ("establishing axioms"). His Instances of the Fingerpost are explicitly at the forks in the logical tree, the term being borrowed "from the fingerposts which are set up where roads part, to indicate the several directions."

Many of his crucial experiments proposed in Book II of *The New Organon* are still fascinating. For example, in order to decide whether the weight of a body is due to its "inherent nature," as some had said, or is due to the attraction of the earth, which would decrease with distance, he proposes comparing the rate of a pendulum clock and a spring clock and then lifting them from the earth to the top of a tall steeple. He concludes that if the pendulum clock on the steeple "goes more slowly than it did on account of the diminished virtue of its weights . . . we may take the attraction of the mass of the earth as the cause of weight."

Here was a method that could separate off the empty theories!

Bacon said the inductive method could be learned by anybody, just like