The Principles of Humane Experimental Technique

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CHAPTER 6

REDUCTION

Many laws regulate variation, some few of which can be dimly seen, and will... be briefly discussed.

Reduction and Strategy in Research

Desirable as replacement is, it would be a mistake to put all our humanitarian eggs in this basket alone. The progress of replacement is gradual, nor is it ever likely to absorb the whole of experimental biology. Refinement may reach such a pitch that a given procedure employing animals is absolutely humane, but in any given field there is bound to be a latent period before such success is attained. Moreover, we have suggested that reduction is desirable in any procedure, however directly humane, which employs large numbers of animals in one laboratory. For all these reasons, reduction remains of great importance, and of all modes of progress it is the one most obviously, immediately, and universally advantageous in terms of efficiency.

One general way in which great reduction may occur is by the right choice of *strategies* in the planning and performance of whole lines of research. (Whether game theory--Von Neumann and Morgenstern, 1947--can be of help here is a question we leave to more competent inquirers.) Most of us settle early in our research career on some strategy that appears to suit our temperament, and are liable never to raise the question again. Some discussion of the subject is, therefore, necessary from time to time, and it raises issues which have been debated throughout the history of science.

The main issue has been well put by Hume (1957b, c) in a searching essay. The central problem is that of choosing between trial and error on a grand scale and deductively inspired research. The second alternative may take the form of testing deductions from well and consciously formulated hypotheses, or it may involve working from hunches--really the same thing, for where hunches are of any value they are found to have been based on equally precise hypotheses of which the investigator was not fully aware until after the tests (Russell, 1952). It is of little importance whether rigorous formulation occurs before or afterwards. The essence of the second alternative strategy is that particular experiments are *selected* on some basis, other than tables of random numbers, from a larger set of experiments which could have been performed (cf. Ashby, 1956a, c). It is obvious that if all scientific research had proceeded by trial and error we should barely be beginning now. It is also obvious that guided (or, as Hume accurately calls it "insighted") research must be vastly less wasteful of animals, where these are the subjects of investigation.

Hume has assembled a set of examples of the two main methods in action, and his account brings out the fact that trial and error methods are entering science on a grand scale and with considerable acceleration. This is specially true in pharmacology and chemotherapy, and results partly from changes in the organization of research projects, partly from increase in the number of scientists with dilution of fundamental research quality, partly from the current vogue for teamwork (entirely sound in principle), and above all from the virtuosity attained by organic chemistry. A constant and huge stream of new chemical substances is made daily available for investigation, and much research directed to major medical targets--anticancer drugs, antitubercular drugs, tranquilizers, etc.--begins to consist of large-scale testing of the products of the organic chemist. This testing is to a large extent, and often explicitly, random. In this country there has been a laudable tendency for control of the chemists by feedback from the biological laboratory[1], which may have accounted for the great success of British firms in developing new drugs. But this tendency is not always prominent in other countries.

The arguments against the trial and error method have been put forward with cogency and copious illustration by Hume; we need not repeat them here. It is possible that the case can be overstated. When the trial and error method does produce results, it is difficult to establish whether these would have been attained more rapidly by a diversion of effort to fundamental research, which could have provided directional guidance. To some extent, the choice may be overdetermined by sociological factors, such as a glut of competent routine investigators with a flair for technique, combined with a shortage of fundamental scientists to guide their operations.

We may, however, suggest two general conclusions and point to one suggestive fact. First, wherever it *is* possible directly to compare guided and random research, the former is seen to be more efficient. Hume cites an excellent example in antituberculosis research. One laboratory had screened 3,500 organic compounds for antitubercular action, adhering, in their own words, "as strictly as possible", to the random selection of test compounds, and had filtered out eleven substances with the property required. Of these eleven, ten had already been discovered by other workers who had followed a lead of some kind (see critical review by Barry, 1953). Second, where such methods are used, it is desirable in terms of humanity, cost, and effort for the trial and error to be applied to replacing objects. (This condition was indeed largely met in the research just mentioned, most of which was done *in vitro.)* Third, simple mechanical problems set to children are found to be tackled by trial and error in those from 8 to 12 years, and by guided selection of tests in those from 12 to 15 (Piaget, 1953). We do not mean to imply that trial and error is always childish or irrational, but only that the grounds for its use should always be scrutinized with special care. As Hume himself points out, testing a totally new compound to discover what actions (of any kind) it may have is a different problem from that of search for a substance which is to have a prescribed property. The former procedure may have its place in research; it is in this context that the methods mentioned in the last chapter are likely to prove of increasing value.

[1]Cf. The procedural flowcharts in the Royal Society lectures cited.