The Principles of Humane Experimental Technique

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CHAPTER 8

THE FACTORS GOVERNING PROGRESS

This tendency in the large groups to go on increasing in size and diverging in character...

The Sociological Factors

Humanity and Efficiency

Experimental efficiency in the widest sense can be expressed as a balance between time, cost, and efficacy (that is, capacity of the experiments to provide the required information). This is the relative importance of the three factors between laboratories and purposes. Time is of minor importance to the pure research worker, for if a procedure does not give rapid results he is in no desperate hurry, and can always find useful interim occupations. For the pathologist, time may be a matter of life and death. For the big commercial laboratory time is money, but the large scale and planned flowchart may permit shifts and staggers.

Cost is a major consideration for all three main types of laboratory and purpose. In the commercial firm this is precisely because it is commercial, in the pathology and research laboratories because of their often slender budgets.

Efficacy is literally vital for the pathologist. The pharmaceutical firm has standards below which it cannot drop, but may compromise above this level. Inadequate research is wasted research, and cannot be tolerated indefinitely. In applied research, and particularly in developmental work, the relations between efficacy and cost have been treated in a general way by Yates (1952).

If we now consider the three main modes of increasing humanity, replacement methods vary in relation to cost. *In vitro* culture of bacteria is much cheaper than guinea pigs almost from the outset. Tissue culture methods are cheaper when running, but may be costly initially in terms of training and installation. Acute *in* *vitro* preparations of mammalian organs are a little more expensive than live animals, for some apparatus is required besides the animals themselves; but increased precision may entail reduction, and hence save cost after all. The use of higher plant--little more than a suggestion at present--would be cheap except in terms of space, and perhaps rather slow. The other replacement methods usually represent a considerable gain in speed of obtaining results.

Refinement will inevitably increase efficacy, and may incidentally entail reduction as well. If not grossly more expensive in itself (in terms of apparatus and skilled staff), it is always more efficient.

Reduction without impairment of efficacy must reduce costs in one direction, and animals are often the costliest item in the experimental laboratory. But the cost of the reducing measure must be balanced against saving in sheer numbers.

In efficacy, or yield of information, the advantages of humane technique apply almost universally. The correlation between humanity and efficacy has appeared so often in this book that we need not labor the point. There is, however, a more fundamental aspect of this correlation, specially important in research. Science means the operational method--telling somebody else how to see what you saw. This method is one of the greatest of all human evolutionary innovations. It has, however, one drawback. It prevents permanent acceptance of false information, but it does not prevent wastage of time and effort (Russell and Russell, in press). The activity of science is the supreme expression of the human exploratory drive, and as such it is the subject to the same pathology. The scientist is liable, like all other individuals, to block his exploration on some front where his reactions to childhood social experiences are impinged upon. When this happens to the experimental biologist, we can predict the consequence with certainty. Instead of really exploring, he will, in his experiments, act out on his animals, in a more or less symbolic and exaggerated way, some kind of treatment which he once experienced in social intercourse with his parents. He can rationalize this as exploration, and hence fail to notice the block. But in fact such acting out invariably occurs precisely when real exploration is blocked, and must be relinquished before real exploration can begin again. Hence, such experiments will be utterly wasteful, misleading, and uninformative. The treatment of the animals, for one thing, will inevitably be such as to impair their use as satisfactory models. The interpretation of the results will be vitiated by projection. Really informative experiments, *must* in fact be as humane as would be conceivably possible, for science and exploration are indissolubly linked to the social activity of cooperation, which will find its expression in relation to other animals no less than to our fellow humans. (This last relationship has actually been established.) Conscious good-will and the social operational method are useless as safeguards against the mechanism of rationalization[1]. It follows logically that, if we are to use a criterion for choosing experiments to perform, the criterion of *humanity* is the best we could possibly invent. Whether or not we can trace the connection in any individual research, this is a fundamental and inescapable law founded on the key properties of human behavior. If we are satisfied that an experiment is maximally humane, we can be quite sure it is the most scientifically valuable one we could perform. This will apply not only to individual experiments but also to whole research programs. One thing more may be added. The other great progressive human activity is that of art, which is closely related to science as to be virtually the same activity. Thus it comes about that the greatest scientific experiments have always been the most humane and the most aesthetically attractive, conveying that sense of beauty and elegance which is the essence of science at its most successful (cf. Russell, 1956a; Russell and Russell, 1957; 1958; and in press).

Beyond these generalizations, we shall not attempt to go. The costing problem, especially in research, demands the most careful separate treatment. But as a broad basis for discussion, we may assume an extremely close general relation between humanity and experimental efficiency. We are, therefore, essentially concerned in this chapter with the factors governing the progress of experimentation itself.

Flexibility and Communication

In the course of this book, we have again and again encountered instances of long *delay* in the application of existing knowledge to the improvement of experimentation. Some of these instances are highly special, others extremely general. For illustration, we may draw up the following list: belated knowledge of the relative numbers of species used; persistent use of the Friedman test; delay in the initiation of microbioassay; delay in the exploitation of statistical methods; delay in the rationalization of breeding methods for uniformity; delay in the *noticing* of published effects of environmental factors on response variance; delay in the application of psychosomatic principles to experimentation; conservatism in the choice of laboratory species; the guarded approach to several aspects of toxicity testing.

Delays of this kind may be regarded as a sort of inertia, or rigidity, the maintenance of a habit (positive or negative) long after information is available for its correction. In the individual organism, rigidity of this kind has been shown to be associated with *isolation*, or lack of communication between central nervous mechanisms. The relation between the two has been demonstrated with special force and clarity in the mating behavior mechanisms of the clawed frog (Russell and Russell, 1957, and in press). It is entirely reasonable to expect a similar relationship at the sociological level. Indeed this is one of the more fundamental predictions of the very recent science of Darwinian mechanisms, on whose principles this section is largely based (Russell, in press, a, b).

What sort of isolation can occur between what sort of sociological units in the present connection? In the progress of industrial technology, lack of communication between firms has been cited as a source of deceleration (Carter and Williams, 1957). We have encountered a strong feeling in the bioassay world that there is inadequate contact between university research pharmacologists and practical assayists responsible for developing workable routines; this may serve as an instance of isolation between types of laboratory. Lack of communication between different countries with different languages has been illustrated in some intriguing data provided recently by Faegri (1956). He examined the bibliographies of papers written in different languages, and thus obtained estimates of the relative attention each scientist pays to work published in languages foreign to him. All these kinds of isolation are important, but they pale into insignificance beside the great curse of modern science--the division into specializations.

The growth of science has inevitably established an ever-increasing number of more and more specialized departments, on the lines of an adaptive radiation. This inevitable trend is harmless in itself, but only if it is neutralized by adequate flow of information through the system, and adequate concentration on synthetic work across the specialist barriers. Two things are required--skillful communication of their results by specialists, and the provision of a class of avowed synthesizers. Hitherto the latter function has been performed only be a handful of exceptionally able men who foresaw the need, such as Haldane, Hogben and especially Sir Julian Huxley[2]. There are now signs that whole streams of science are coming almost to a halt for lack of what we may quite properly call hybrid vigor. Oppenheimer, for instance, has "expressed the view that the pioneer conceptions which led through Einstein to the splitting of the atom are now inadequate to yield an orderly description of the physical world". He believes that "the man or woman who can rescue us from the rich disorder of our new knowledge" will probably be "someone able not merely to interpret the nuclear scientists, but equally to set that new knowledge in the context of biological science and of the humanities" (Editorial, *Nature,* 1956).

If this is the situation of the advanced guard of science, matters are likely to be a good deal worse in the areas of consolidation--that is, of applied science. The listed instances of delay in experimental progress give support to this view. Conservatism in the choice of laboratory species means an inadequate use of the specialist knowledge of the zoologist. Failure to control the proximate environment in bioassay means failure to use the known principles of psychosomatics either for immediate application or for developmental research, and has conserved the constancy fallacy about variance. To some extent, failure to make the connections arises at the level of the individual. But this is intimately related to the sociological situation. For the gradual growth of awe before experts means that an individual may distrust even his own knowledge and fail to use it, if it has not been acquired at second hand. Respect for expert specialist knowledge should never become uncritical. It may do so readily, in consequence of the pathological craving for stable dominance hierarchies, a craving that can never be satisfied in the conditions of human evolution (Russell and Russell, in press).

The two most instructive instances are those of the inbred line assumption (whose history has been so well surveyed by Biggers and Claringbold), and the progress of microbioassay. For decades, nobody apparently thought of challenging the inbred line assumption, because (we may surmise) it was *thought* to be a clear deduction from existing genetical knowledge, and therefore not to be discussed except by the expert geneticist. But the geneticists of the early thirties never thought of intervening, because (we may surmise) they did not know what was going on in bioassay, and because it would never have occurred to them that anyone could still think in terms of a purely additive relation between genotypic and environmental sources of variance. Failure of communication between two specialist groups thus has two serious consequences. Not only do the current ideas of the one fail to penetrate the other, but the *past* (or even completely misinterpreted) ideas of the one may act as a rigid barrier to advance in the other. For the assayists could perfectly well have challenged the assumption on the basis of their own empirical results, without reference to the geneticists at all. Thus, awe of a specialist department, together with failure to keep in touch with it, could lead men to distrust the evidence of their own observations. This is specially likely to happen when, as here, the two departments are respectively "pure" and "applied", for this dichotomy is itself the most tenacious of all the specialist divisions. A really intense interest in the theoretical basis of hybrid uniformity did not arise in genetics itself until the fifties. Many assayists, surely, must have made the observation of Emmens without reporting it. Had the assayists of the thirties had the courage of their convictions, they might have called to the attention of the geneticists themselves a set of facts of great theoretical interest.

Microbioassay affords a welcome contrast. True, there was some delay, perhaps mainly due to technical difficulties, as in the parallel case of virology. But the outburst of progress is the most impressive feature of this area. This is entirely to be ascribed to free intercommunication between the specialists of animal nutrition and microbiochemistry, to the great benefit of both. Neither hesitated to approach the other.

The problem of interspecialist communication merges into the general one of information retrieval. We now have far too much information as a species to digest as individuals. To those engaged in library and documentation work, it has long been apparent that the retrieval problem can never be solved except in statistical terms (see the great work of Bradford, 1953, 2nd edition). If we seek the published information on any subject, however small, we can never hope to recover more than a finite proportion of it. Publications on any one subject are spread through the vast mass of periodicals in accordance with a definitive law. Briefly, there will be many such in a few periodicals and few in a great many. Search of the few periodicals at the focus is easy, but the penumbra of information is spread through a host of increasingly remotely related periodicals. There is one important practical point here. The number of scientific *books* published annually, though great, provides a total of matter far, far smaller than that scattered in the periodicals. The book is, therefore, still the most efficient means of interspecialist communication.

The retrieval problem becomes still more formidable when *technique* is concerned, as Visscher has pointed out (1951). "In general, methodology is usually relegated to a place of smaller type and sharply abbreviated importance in journal publication of research. Numerous essential details are customarily omitted, either because they are considered to be common knowledge, or simply for lack of space." One of the most useful ways of countering specialization is for the individual scientist to work experimentally in several different fields. Visscher points out that the individual is often prevented "from full exploitation of a field because of unfamiliarity with the variety of methods of study which would be useful and essential to such full study".

One approach to this special problem is to concentrate some attention on the particular branch of synthesis which takes the form of general methodological study. (This is perhaps the main justification of the present book.) Such studies not only help to bring scattered facts into juxtaposition, they also encourage the individual worker to lose his terror of experts in other fields, to confront them whenever possible with the problems raised in his own, and to seek their help when it will be most useful. There is already one group of specialists who are used as specialists should be--the statisticians. They already normally work in close touch with experimentalists. The latter have all the benefit of guidance at the start and analysis at the end of their investigations. The statisticians are constantly supplied with concrete problems to stimulate their treatment of general aspects of statistical theory and method. This trend could be extended with profit. Wherever possible, specialists should not be segregated in separate laboratories. The aim should rather be to assemble as many different kinds as possible under one roof. This condition is satisfied to some extent in Group II laboratories, for it has been found by experience to be quite indispensable in research[3]. Faced with the inexorable conditions of retrieval, we should also be encouraging the training and use of specialists in the general, or at least specialists in problems which cut across the barriers of subject matter.

One way of looking at this is to see the necessity for research on research, or "research on methods of research" (Medawar, 1957), or "operations research looking at research operations" (Johnson, cited by Hiscocks, 1956). This is becoming apparent to many research directors, as appeared at the recent conference reviewed by Hiscocks in the work just quoted. There seems also to be a place for whole organizations directed to this end, the equivalent of industrial consultants. We shall mention a few such organizations presently. As science continues to expand, this will be seen more and more clearly as the only way to save it from grinding to a standstill.

For our present subject, several special factors are important against this general background--problems of education, problems of law (always behind the scenes in applied science), and the special organizations concerned with method. With little more than a mention of each of these sociological factors, we may conclude this survey.

Educational Aspects

Formal education can contribute to experimental progress in two ways. First, it might create more specialists in method; but this is a matter of very high level policy. Second, and more immediate, every effort could be made to encourage wide knowledge and interests in the education of, for instance, pharmacologists and pharmacists. Our survey has shown that study of some special fields is of particular importance. Thus every effort should be made to impart to the future experimenter some familiarity with comparative physiology, animal behavior, and psychosomatics. But an important proviso now appears. Throughout the book we have assumed that the practical pharmacologist and the research biologist. This is far from true in practice. The experimental pathology department is often the Cinderella of the hospital. The enormous prestige of organic chemistry leads to control by chemists of pharmacological research and even routine policy in many commercial firms. The experimental biologist is not a free agent, and it is difficult to assess how much this factor may be delaying progress. It would be idle to equip him for maximal efficiency if he has too little say to make use of his equipment. Educational policy, therefore, must concern itself with others as well--medical people in general, for instance, and, above all, chemists. If the latter are at all likely to engage in pharmaceutical work, they should be given, at the university or technical educational institute, at least a glimpse of those aspects of biology which will govern the conditions under which they are to work. And since in all scientific activity administrators play their part, the educational problem here cannot be considered in isolation from the very general question of higher education itself. The aesthetic aspect of experimentation might one day take its place among what are curiously and selectively called the "humanities". The thought has a certain piquancy in the context of what we call humane technique.

If any activity is so specifically human as to take first rank among "humanities", it is that of science.

Legal and Semi-Legal Aspects

In another, more important way, the pharmacologist is not a free agent. Many have pointed out to us that they would be making a number of practical improvements, were it not for the law.

The (British) law in this area centers on the Therapeutic Substances Act of 1956, with a number of regulations and orders made earlier in the fifties. (All these are published by H.M. Stationary Office--Statutory Instruments 1952, Nos. 1933, 1937; 1953, Nos. 1172, 1173; 1954, Nos. 1645, 1646, 1647, etc.) These instruments control the conditions of purity of standards, and above all those of toxicity of preparations used in human and veterinary medicine. As such, they determine the limiting conditions for both replacement and reduction of experimental animals. If they lag behind knowledge, they are liable (e.g.) to cause animals to be used for toxicity testing where this is no longer necessary (owing to better or better understood preparation methods), or to specify larger numbers than currently necessary. There may also be some general fallacies underlying some of these provisions, such as an overestimate of the effect of error in assay through failure to take account of much greater variance in individual human physiological responses. (Man is, physiologically, the most variable of all species mainly on account of the huge contribution due to variation in his central nervous system.) In certain conditions, "any minute precision in the assay... will be swamped by the variance of the patient's response, and no advantage to the patient will accrue from it" (Hume, 1957c). Hume gives a numerical example, and concludes thus: "The question arises, therefore, whether some of the standards laid down by regulation under the Therapeutic Substances Act are not unrealistic; whether, in fact, a proportion of the animals used in that connection are not wasted." It is a prerequisite for the progress of humane technique that the law in this area should be kept fully rational and fully up to date. It cannot be too widely recognized that legislation and regulation here need constant attention, and that experimental biologists should be constantly reassessing policy in advance, in order to make the necessary recommendations without undue loss of time. It is also important that everyone should realize the conditions and restrictions under which the experimentalist, and his administrative colleagues, operate. All this is specially important in toxicity testing, and such phenomena as the high-fidelity fallacy may be more prevalent and influential at the legal rather than the laboratory level.

There are more nebulous restrictions of a semi-legal nature. There are some specifications which can be violated without legal penalty. These may still be adhered to because of the very slight risk of accidents, which could be disastrous for a firm that admitted to relaxing the rules (even if this relaxation was *not* responsible for the accident). Some of these rules may be over-cautious. Rules of this kind are provided by pharmacopoeial publications, which are indeed repeatedly revised, but at intervals of several years. Such instructions are explicitly nonlegal, but naturally have the consequences mentioned. These difficulties might be diminished by an authoritative and widely representative committee (such as that responsible for the *British Pharmacopoeia* and its supplements), if it could pronounce a little more frequently. As it is, the repeated revision is doubtless extremely valuable in this connection.

[1]In the pathological sense of the term.
[2]There have been some very recent developments in this context, notably those of *general systems theory* and *behavioral science*, which, together with cybernetics, make up a sort of superscience (cf. Bertalanffy, 1956; Miller, 1955; Gerard *et al*, 1956; Russell, in press, b).
[3]Some of the greatest achievements of modern American science, especially, have come about through such assemblies, periodic or permanent. The cybernetic movement itself is the crowning example.