Natural kinds, natural history and the clinician-researcher

B.G. CHARLTON

From the Department of Psychology, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Summary

Recent medical research has been based on a flawed rationale of clinical innovation (here termed the ‘basic-to-mega model’) which neglects the human organism as a vital focus of clinical scientific study. The consequent over-concentration upon cellular and population levels of analysis has probably damaged the rate of therapeutic progress. The key role in medical research should be acknowledged to lie with clinician-researchers whose ‘experimental animal is the patient and whose ‘end-points’ are health and disease. The distinctive strength of the clinician-researcher derives from an ability to combine understanding of the ‘natural kinds’ (i.e. true biological categories) relevant to human disease, with experience of the ‘natural history’ of disease (i.e. its longitudinal pattern, including the response to interventions). Such knowledge is explicitly formalized by the activities of clinical science and clinical epidemiology. A sufficient supply of active clinician-researchers is the catalyst of innovation, and an insufficient supply is currently a rate-limiting factor in therapeutic progress.

Introduction

Medical research over the past two or three decades has been damaged by a neglect of clinical science and of clinical epidemiology which has the individual patient as its primary unit of analysis. Instead of focusing upon the human organism and human pathology, the dominant research paradigms (which attract the bulk of status and funding) are ‘basic’ cellular and molecular biology on the one hand, and large (‘mega’) population epidemiology on the other. Although both these strategies are extremely important in their own right, and remain vital to medical progress, they are usually of subsidiary importance to clinical research when it comes to generating large-scale therapeutic improvements. No combination of knowledge derived from cells and populations can exclude the need for a knowledge of patients.

A false model of the path to therapeutic progress

Medical research is currently operating on the basis of a false rationale of the path to clinical innovation; which might be termed the basic-to-mega model. The prevailing belief is that increased understanding of biological mechanisms (generated by basic science) will combine with information concerning effect sizes (derived from very large epidemiological surveys, follow-ups, mega-randomized trials and meta-analyses) to produce continual advances in therapy. The implicit hope is that researchers can somehow map directly from the highly-controlled experimental level of ‘pure’ biology onto the statistically precise level of summary data from large group studies, while altogether missing-out the scientifically tangled and ethically troublesome level of clinicians dealing with sick human beings.

But the expectation that this basic-to-mega model of research would maintain and accelerate therapeutic progress has been largely unfulfilled. Despite massive increases in medical research effort and funding, there has probably been a significant decline in the rate of significant clinical breakthroughs when recent decades are compared with the ‘golden age’ of the mid-twentieth-century therapeutic revolution.
For example, this deceleration in major innovation has recently been thoroughly documented in the field of psychiatry and psychopharmacology. Work in progress evaluating clinical effectiveness across the wide range of medical activity suggests that a similar decline is probably to be seen in many other fields (personal communication, James Le Fanu). While the precise factors behind this putative decline remain uncertain, it seems likely that any significant enhancement of therapeutic progress will depend on a renewed recognition of the crucial importance of clinician-researchers.

**Natural kinds**

Progress in medical research is underpinned by a classification system which identifies the natural kinds associated with disease and enables relevant observations to be generalized with validity. In principle, there are an infinite number of ways to classify phenomena. Natural kinds are those classes that constitute a true (i.e. approximately real) working-model of relevant entities and the causal pathways that connect them.

The natural kinds of most direct relevance to the practice of medicine are those applicable to diagnosis (nosology). An ideal nosology would correspond to natural kinds—biologically real disease entities. Historical categories such as possession by evil spirits, ague and dropsy, were not natural kinds (although presumably they had pragmatic, social or therapeutic usefulness). Patients that inhabited this kind of pre-scientific category were aetiologically, pathologically and prognostically heterogeneous; despite any superficial similarities. (A similar situation probably prevails for current syndromal psychiatric diagnostic categories such as schizophrenia and depression which, despite their considerable heuristic value, have—arguably—held back scientific research and clinical innovation for some decades.)

As nosology approaches more closely to a system of natural kinds, it typically becomes more useful. The category of fever is modestly helpful as a guide to symptomatic treatment, but classifying fevers into organ-based infectious causes such as pneumonia, cystitis and cellulitis, enables a degree of prognostication. Further categorization in terms of necessary causal infectious agents provides prognostic refinement, and has implications for specific therapy. And as well as these benefits to management, natural kinds provide the fundamental basis for research into the natural history of disease.

**Natural history**

Natural kinds are only half the story of clinical research: they provide the basis for generalization, but are of little value without a corresponding knowledge of natural history. The natural history of a disease is its longitudinal course, progression and pattern—outcomes with and without treatment, and comparing the outcome after different treatments. It is by observing its effect on natural history that a clinician is able to decide whether a putative therapeutic intervention is worthwhile. Exploration of natural history is the core activity of clinical epidemiology.

Knowledge of natural history can lead to therapeutic progress only when it moves hand-in-hand with a knowledge of natural kinds: natural kinds describe the character of those entities to which natural history properly refers. The natural history of false categories such as ague and dropsy has little value in clinical management or investigation. In the development of modern medical science, reliable knowledge of natural history grew only after the true structure of the human organism had been elucidated by the nascent science of anatomy.

Determining the natural kinds relevant to clinical epidemiology is the essence of clinical science and the particular function of the clinician-researcher. This necessity arises because only a tiny part of the knowledge generated at the cellular level is significant for the treatment of human disease. Given the sheer number and complexity of interacting pathways, it is unlikely that the biological importance of a pathway will predict its clinical importance as a target for intervention. Typically, the clinically important point of intervention will only emerge when the relevant experimental animal is studied, i.e. the whole human organism.

The problem with large-population epidemiology is, in a sense, the opposite to that of basic science. Large population mega-epidemiology studies natural history, but the large population entities it studies are seldom true natural kinds. Large populations (such as those that form the unit of analysis in mega-randomized trials and meta-analysis) comprise aetiologically, pathologically and prognostically heterogeneous patients, and they are exposed to a similarly diverse mixed-bag of therapeutic interventions. Summaries of dissimilar entities and mixed causes are statistical artifacts, not natural kinds. Hence, population-level studies that do not operate at the level of natural kinds are clinically inapplicable or misleading when applied to individual patients.

**Contribution of the clinician-researcher**

It is the ranks of clinician-researchers (along with industrial chemists, pharmacologists and other ‘inventors’) who have usually supplied the artistry
The clinician-researcher

Clinician-researchers are, it has been argued, vital to the continued progress of medical therapy, yet at the same time they are a species in danger of extinction. It seems the obstacles that active clinician-researchers need to surmount are continually increasing: lack of a training and career structure, short-termism and inappropriate measures in research evaluation, the organizational separation of hospitals and universities, and the increasingly restrictive practices of ethical and regulatory committees, to name but four. Even if such obstacles are overcome, clinical scientists are undervalued by the academic research establishment, funding bodies and health services to a degree that is astonishing when one considers their achievements and potential. Basic medical scientists and mega-epidemiologists seem to scoop most of the credit.

A new medical research strategy is required. Study of the individual human organism and its pathology needs to be acknowledged as a scientific activity indispensable to the significant medical breakthroughs from which all will benefit. It is timely to emphasize that clinician-researchers are major catalysts of therapeutic progress, and a rate-limiting step in generating major medical breakthroughs. As things stand, clinician-researchers are an endangered breed, at risk of extinction. Special provision may be required even to ensure short-term survival. In the longer term, they will probably need a protected habitat.

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References