Commentary: Complex disease—responding to the challenge

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The thought-provoking paper by Buchanan et al.,\(^1\) raises fundamental questions. Has epidemiology passed its zenith? If so, why? And what should be our response?

In its early years, epidemiology generated many important discoveries, but despite more sophisticated methods and much greater investment of resource, output over the past two decades has been less remarkable. This could be because today’s epidemiologists are less competent than their predecessors, but while there is no doubting the innovation and application of those who pioneered the discipline, a substantial decline in standards seems unlikely. A more plausible explanation is that nowadays, major discoveries are harder to make.

Buchanan et al. attribute this to the complexity of the diseases that we now address, drawing a contrast with disorders resulting from simple Mendelian inheritance, infection, or environmental toxins, for which it is possible to identify a single causal agent that is both specific and highly predictive. When a cause of disease is both necessary and sufficient, or nearly so, it should be easier to spot and confirm. However, causes that do not satisfy this strict requirement should still be readily demonstrable if they carry a high relative risk. Exposure to aromatic amines is neither necessary nor sufficient as a cause of bladder cancer, but the relative risk is high, and with the appropriate study design, was clearly established.\(^2\) Thus, although by Buchanan’s definition, bladder cancer is a complex disease, it has, nevertheless, been possible to make useful progress in its prevention, if only for a subset of the population.

The limit to important new discoveries is not the complexity of disease as such, but the number of unrecognized causes that carry high relative risks. Exposures carrying large and statistically robust relative risks for chronic diseases do still come to light from time to time—for example, the risk of malignant melanoma in people with multiple benign moles,\(^3\) and the risk of knee osteoarthritis in relation to obesity.\(^4\) However, it is unusual for a new risk factor affecting large numbers of people to be confirmed as carrying a relative risk \(\geq 2\) for a major disease.

Epidemiologists have responded to this challenge in various ways. One approach has been to conduct very large studies with detailed assessment of exposure to a wide range of known and suspected risk factors and then to apply advanced statistical techniques in an attempt to distinguish their independent effects. With this method, even relative risks \(<1.5\) can be statistically significant, and by careful control for potential confounding factors the chance of inappropriate causal attribution should be minimized. In a few cases, the findings have been sufficiently consistent across a number of studies that they have achieved wide acceptance and have formed the basis for public health policy. An example is the regulation of particulate air pollutants, which even at relatively low concentrations, have been found to carry a small but consistently increased risk of cardio-respiratory mortality.\(^5\)

But even when multiple, carefully controlled studies produce similar results, caution is needed if relative risks are small. Observational studies strongly suggested that beta carotene protects against cancer and that hormone replacement therapy protects against coronary heart disease, but neither of these findings was confirmed when randomized intervention studies were carried out.\(^6,7\) Presumably, the problem lay in unrecognized residual confounding.

Another ploy has been to exploit technological advances that allow new exposures to be studied. The most salient example is the use of genotyping in genetic studies. Here, there is less potential for bias and confounding than in other areas of epidemiology, and lower relative risks can be interpreted with greater confidence.\(^8\) Some findings hold promise of useful therapeutic applications. For example, demonstration that asthma and bronchial hyper-responsiveness are linked with a gene, ADAM33, that codes for a membrane metalloprotease, has opened up the possibility of new pharmacological targets.\(^9\) Overall, however, the return from substantial research effort over more than 10 years is disappointing when set against what was achieved by a small number of epidemiologists in a single decade from 1950.

A third strategy has been to focus on diseases that in the past received less attention because they were relatively rare or regarded as less serious. Here, some useful advances in understanding have been achieved, such as the unusually high risk of hip osteoarthritis in farming and other occupations that entail frequent heavy lifting.\(^10\) But even for these previously ‘neglected’ diseases, it has not always been easy to identify causes carrying high relative risks.

Overall, therefore, there has been an increase in activity, but in proportion to the outlay of time and money, fewer important discoveries. Clearly, there is a possibility of disenchantment. Funding bodies may become less inclined to invest in epidemiology, and it is notable that currently the largest single epidemiological initiative in the UK, the Biobank project, depended for its support on backing from the powerful genetics lobby. In Britain, this threat to funding is particularly worrying because it coincides with an increasingly restrictive research environment. Primary research in epidemiology is becoming progressively more difficult because of concerns about data protection, ever increasing emphasis by ethics committees on the personal autonomy of potential study...
participants, disproportionate complexities of research governance, and growing reluctance of the public to participate in research when they are perpetually bombarded with commercial surveys by both mail and phone. A consequence is that studies have become more expensive, the biggest proportionate increase being for smaller and simpler investigations.

How should we respond? First, we must be clear what we are trying to achieve. Is the ultimate aim to understand exactly why one person gets a disease and another does not? If so, as has been argued elsewhere, success is unlikely.11 In many cases, whether or not someone develops a disease may depend on combinations of events at a molecular or cellular level that we can never hope to measure. And even if a causal factor systematically increases the risk of disease by 50%, this will be difficult to demonstrate with confidence by epidemiology. At best we might hope to obtain clues to causation that can be tested in other ways.

The alternative is to view epidemiology not as a means of understanding the natural world but as an applied science, which can help to form practical decisions in the prevention and management of illness. This goes back to its roots. When John Snow carried out his research on cholera, his principal goal was the prevention of disease and not the advancement of scientific knowledge. And there are many areas of public health and clinical medicine that require epidemiological input. How should we respond most effectively when new infectious diseases such as SARS emerge? Does new technology such as mobile telephony pose health risks that require regulatory control? What are the most appropriate restrictions on driving for patients with epilepsy? In responding to questions like these, it does not matter if answers cannot be definitive. Decisions must be made on the best information that is available.

Linked to this, there is a continuing need for effective systems of health surveillance so that new problems such as AIDS can be detected and investigated in timely fashion. Surveillance systems also provide a check on the effectiveness of control measures. For example, the continuing increase in mortality from mesothelioma in Britain is an indication either that earlier limits on asbestos exposure were unsatisfactory or that they were inadequately implemented.12

In picking on aetiological hypotheses to investigate, we need to be more discriminating. The key to many of the most important epidemiological discoveries has not been an advance in technique but asking the right question. A good example is the demonstration that risk of sudden infant death is importantly reduced if babies are placed to sleep on their back.13 Once the hypothesis had been conceived, testing it was not too difficult and did not require complex methods.

Of course, identifying good study questions is easier said than done, but there are helpful pointers. One situation with the potential to be more fruitful occurs when the incidence of a disease is increasing. As Buchanan and colleagues point out, such trends must have environmental causes, and if the increase in incidence is large (as, for example, with testicular cancer14), then those causes are likely to carry high relative risks. In addition, some types of exposure offer more promise than others. One of the most fruitful areas for epidemiological research in recent decades has been the hazards associated with pharmaceuticals. Not only can relative risks be fairly high but also exposure is easier to ascertain than for many other risk factors.

Moreover, the associated burden of disease may be large, as for example, with myocardial infarction and rofecoxib.15,16

Finally, we should extend our horizons to endpoints other than disease incidence and mortality. For example, one area that is of immediate practical relevance, and much in need of further research, is the distribution and determinants of people’s personal exposure to chemical pollutants in the environment. Here, the outcome of interest may be an internal dose measured by a biomarker and the risk factors different aspects of individual lifestyle and environment. Thus, it has been shown that residence near a petrochemical plant had negligible impact on an individual’s uptake of benzene in comparison with active smoking, living with a smoker, frequently filling a car with petrol, or driving in traffic.17 This information is extremely useful in responding to leukaemia clusters near to refineries.

In summary, epidemiology still has much to offer, but we cannot expect it to provide a complete understanding of why some people get a disease and others do not. Nor should we expect major discoveries to occur with the same frequency that they did in the 1950s, 1960s, and 1970s. However, by focusing on questions of immediate practical importance, together with judicious selection of more speculative hypotheses for exploration, epidemiologists will continue to make a telling contribution to public health.

References

Commentary: Rethinking epidemiology

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Introduction

It is time, we are told, to rethink epidemiology. It is time to rethink our quest, our concepts, and the nature and origin of our commitments. That is a lot of thinking, stretching across the broad landscape of our professional practice. Even our metaphors—this blind quest for the Philosopher’s Stone1—should be rethought, as well as our concept of cause, our much-maligned criteria of causation, our signature methods, and, it seems, our philosophical foundations. It is time, we are told, to step away from all that is associated with the natural laboratory of observational science, once the source of so many successes but now fraught with ‘profound and fundamental problems’, to use the precise language of Drs Buchanan, Weiss, and Fullerton.

This is no ordinary rethinking. We need innovative, creative, out-of-the-box thinking, for we have been, to borrow a few familiar phrases, barking up the wrong tree, beating a dead horse, dreaming an impossible dream.

It has been 5 years since the human genome was mapped. Long enough, it seems to Drs Buchanan, Weiss, and Fullerton, to determine that epidemiology cannot fulfill the promises that were made: the improvements in diagnosis, prevention, and therapeutics and a new kind of medicine that focuses on the ‘very essence’ of individual lives, guiding each of us along our unique trajectory, predicting precise risks for each and every one of us.2 Epidemiology, we are told, cannot even provide society with the kind of knowledge science itself expects: consistent, reproducible results about the causes of all kinds of important concerns, such as cancer, heart disease, stomach ulcers, colds, autism, schizophrenia, syphilis, health care costs, healthier Americans, even aging, and, in the words of Drs Buchanan, Weiss, and Fullerton, ‘you name it’ when it comes to the causal effects of genes.

Apparently, epidemiology was once a legitimate science of disease causation, but no longer. Who has not heard that we have found all the strong associations, with only the weak left to be discovered? To these dubious assertions about the past and not-yet-tested prognostications of the future, Drs Buchanan, Weiss, and Fullerton add a particularly chilling condition: even very large cohorts like those proposed for the Human Genome Project and by the investigators developing all those ‘biobanks’, cannot help the situation.3 The underlying structure of biology connecting genes to individual traits—the ‘hour glass’ with gravity-defying grains of sand—prevents us from understanding anything new about weak biological effects using epidemiological studies.

Small wonder we must rethink epidemiology, trying to understand how things could have gone so wrong in a present that is exploding in our faces. Let us begin by rethinking our quest: the metaphorical search for the Philosopher’s Stone.

Rethinking the quest

We are not stuck, it seems to me, behind thick wooden doors in some medieval ivory tower, hunched over bubbling potions in an alchemist’s hideaway, futilely experimenting with one