COMMENTS

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Evidence-Based Medicine and the Need for Non-Commercial Clinical Research Directed Towards Therapeutic Innovation

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I have spent much of my medical life in schizophrenia research, and I am frequently consulted by colleagues who have a schizophrenia problem in their family. Recently, I was contacted by a distinguished medically qualified statistician, a prominent enthusiast for evidence-based medicine. His 19-year-old son had received a diagnosis of probable schizophrenia and my colleague wanted to discuss treatment with me.

Given his background, I naturally referred him to the many reports from the Cochrane collaboration on the efficacy and side effects of anti-schizophrenic drugs. I also pointed to perhaps the most comprehensive report of all, the recent paper on the FDA database on antipsychotic pharmaceuticals (1). I provided to my colleague a substantial package of well-conducted studies, providing much evidence that might enable him to draw conclusions.

A few days later, my colleague called again, thoroughly disenchanted. He had no experience of psychiatry other than casual sightings of drug advertisements in general medical journals. He was dismayed to find how little progress had been made. On standard rating scales, the FDA dossier showed that the average improvement produced by drugs introduced in the 1960s was 17%, whereas with the drugs introduced in the 1990s it was 16%! The movement disorder side effects of the early drugs had been greatly reduced, but only to be replaced by possibly even more dangerous metabolic and cardiovascular side effects. The evidence base not only showed that the new drugs had much smaller overall effects than my colleague had imagined, but it also gave no specific guidance as to what might be done for an individual patient. All the trials had been conducted on patients whose situations bore only a distant relationship to that of my friend's son.

"What would you advise?" my colleague asked. I laughed and gently pointed out that his question was a negation of much of what he stood for professionally. He had sifted the evidence thoroughly. He had learned what many doctors learn when they or members of their families become ill: the evidence base for many illnesses remains appallingly weak if one expects it to be reliable guide of value to the individual doctor caring for the individual patient.

This episode made me think about some of the weaknesses in our modern evidence-based practice. If one looks at the medical interventions we have for many diseases, whether they be psychiatric or neurological disorders, cancer, cardiovascular or respiratory or gastrointestinal problems, or almost any type of illness other than bacterial infections, what evidence-based medicine shows is that, as my colleague found, many of our interventions are pitifully inadequate. Our studies, although beautifully conducted, have been done on patient populations that bear only a limited relationship to those patients we actually see. The number needed to treat to achieve one success over and above that which could be achieved by placebo may be 10, 20, or even as high as 50. Thus, the trials actually give us almost no guidance as to the likely outcome of an intervention in the individual patient who sits in front of us. For many conditions, therapeutic effects are so small that neither the patient, nor the relative, nor the doctor is likely to be able to recognize any differences in the patient's state as a result of our intervention. We pride ourselves on our large, well-conducted, immaculately analyzed trials that give significant results. But we have forgotten that we need to conduct

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such enormous trials only because our interventions are so minimally effective. If we were making a really large difference to the outcome, small trials would suffice and provide clearly significant results.

Why are we doing so badly while living with the illusion that we are doing so well? Why are the outcomes of medical treatments in 2002 for the most part only marginally better than the best treatments available in 1965, whereas many 1965 treatments were often truly and dramatically better than the best available in 1930 (2, 3)?

I stumbled on part of the answer while reading an obituray of Heinz Lehmann, the psychiatrist and psychopharmacologist (4). In the early 1940s, he became the psychiatrist at a large Canadian hospital with one nurse to assist in his research. Yet over the next 20 years, he carefully tested over 20 novel therapies and was responsible for the first North American studies of tricyclic antidepressants, antipsychotics, and lithium. If he could not see an important clinical effect in 10 to 15 patients, he discarded the therapy; however, if he did see an effect, then he became a great enthusiast.

Of course Lehmann's approach would be impossible now. He did not have to argue his case before an IRB before starting a study, he did not have a statistician telling him that it was unethical to do trials inadequately powered to detect small effects, he did not have an army of experts of all types with whom he had to consult. He thought that good drugs should have big effects or they were not worth bothering about and he required no funding other than the cost of his own time. His patients were not being sought for large drug industry trials where revenues per patient might be anything from $3,000 to $30,000 depending on the complexity and duration of the trial. His institution was not pressuring him to come up with external funding to support his research activities.

As almost any physician who becomes sick personally, or who has a sick friend or relative knows, many of our present medical interventions, although wonderfully documented, are not very effective. With some obvious exceptions, like peptic ulcer pain, infections by many bacteria, pain in general, or acute asthma, it is difficult for either the doctor or patient to attribute with confidence any change in condition to a drug effect. This is because often only 5–20% of patients benefit more than those given placebo. What we desperately need in medicine are medications that work 80–100% of the time and where effects are so dramatic that neither doctor nor patient can have any doubts about the impact of treatment.

We are not going to get such medicines by present clinical research methods, though, or we will be very lucky if we do. There is mounting evidence that for all of its sophistication and regulation—or perhaps even because of these things—the drug industry research effort is failing. The top 20 companies need each year to introduce between one and four drugs with potential annual sales of $500 million or more in order to sustain growth: none is coming close and most are failing miserably (5, 6). By my estimation, one of the top five companies, together with the companies it has taken over, has spent around $30 billion over the last 12 years or so without coming up with a single important new drug. All of the compounds in its portfolio either originated before 1989, are me-too copies, are trivial line extensions, or are licensed-in. To date, there is little evidence that genomics-based medicine is going to make any difference (5, 6). How can so much money be spent—or wasted—without real patient benefit?

We can learn something by looking at how things were done between about 1930 and 1960 and watching people like Lehmann at work. Almost all drugs then resulted from rapid and effective iteration of development involving chemists, whole animal pharmacologists, and clinicians. Very large numbers of approaches were tested on what, by modern standards, were very small numbers of patients. Big effects were sought: drugs that did not have an obvious effect on patients were discarded and undoubtedly many compounds of modest efficacy were missed. But overall, the results were spectacular and the practice of medicine was irrevocably changed (2, 3).

The main changes in clinical research between then and now are the enormous costs of trials per patient enrolled, the obsession with large trials to ensure that small effects are not missed, and the need for a huge basic science and pharmaceutical technology dossier before anything can be tested. No clinical scientist is now likely to test more than two or three drugs in a lifetime of research, as compared with Lehmann's average of around one a year during his active period. No drug that does not have the support of a substantial company is likely to be funded. No drug can attract such corporate support unless it is fully patent protected. In this climate, there can be few trials of nutrients or biochemical intermediates, of novel uses for old drugs, and of natural products, which were all major sources of past therapeutic success. We have taken drug discovery procedures from patient-orientated clinicians and handed them over to large bureaucracies who will work only with patent-protected products that give an adequate financial return. No wonder that real progress is so slow.

There is a need for large-scale trial organizations that will tease out marginal adverse or therapeutic effects of those drugs that will not generate detectable changes in outcome in the individual patient. When the number-needed-to-treat (NNT) rises above 10 or so, such trials are clearly necessary. But what patients want—and sooner or later all doctors, basic scientists, pharma industry professionals, and regulators will be patients— is a drug where the NNT is one or two! The only way we are going to get such drugs is to make a series of honest admissons:

1. Progress over the last 30 to 40 years has been pathetic compared with the 30 to 40 years before that.
2. Something has gone seriously wrong with the drug discovery process in the pharmaceutical industry, and

the astronomical costs of drug development have ensured that drugs are unlikely to come from anywhere else.

3. The failure means that like almost all previous generations of scientists, we have overestimated the completeness of our knowledge (5). I once heard Howard Florey, the Nobel laureate developer of penicillin, state that, in his view, in biomedical science the ratio of the unknown to the known would always be close to infinity. I suspect he was and is right and that the present hubris of the enthusiasts for the human genome project will be seen to be precisely that. Our illusion that our knowledge is near-complete may be drastically limiting our scientific and medical innovation.
4. We must therefore test many more drugs of many more types in many more small trials that look for large effects.
5. To do so, we must reverse two trends. One is the depressing and seemingly inexorable decline in the numbers of research-oriented clinicians and clinically-oriented basic scientists (7). At the same time, we must greatly reduce the institutional and financial barriers to clinical research, and so enable many more small trials to be conducted. We must do many of those trials on concepts and products that are not—at least initially—supported by the pharmaceutical industry.

The escalating costs of the health care system will bankrupt both states and individuals. These costs largely arise because we are spending vast amounts on marginally useful treatments that ensure that patients return to the health case system again and again. The only way this will change is if we find dramatically effective treatments that remove patients from the health care system altogether. And the only way to make such discoveries will be to test greater numbers of scientifically much more diverse approaches to treatment. That, I believe, is the ethical imperative of all involved in medical research. And because the introduction of highly effective treatments is the only possible basis for a dramatic reduction in costs, it happens to be a financial imperative as well.

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