Why are we doing so little clinical research?
Part 2: Why clinical research is neglected

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In Part 1, I described clinical descriptive research as observing, recording, classifying, and analyzing, and expressed puzzlement at our neglect of it, given the notable contribution made by family physicians in the past. Clinical research seems to have been replaced by survey research for studies in family practice.

A recent article in *Family Medicine*[1] showed that, by far, the most common type of research done by family medicine residents at the University of British Colombia has been the cross-sectional population survey. In view of the time constraints, this is not surprising. But I believe this is also the case in our discipline as a whole as noted by editors of *Canadian Family Physician*.[2] Surveys have their place, but we cannot base a credible clinical discipline on them.

Besides the obvious disincentives to long-term projects, I can think of four reasons for our neglect of clinical research.

Misunderstanding the structure of medical knowledge. The common assumption about generation of knowledge is that the interaction of basic and population sciences gives us knowledge of disease mechanisms, causes, and therapeutic tools. This knowledge is then tested in clinical trials. Our knowledge of cardiovascular risk factors is a case in point. Laboratory science identified lipidemia as a possible risk factor, population studies confirmed it as a risk factor, and laboratory science developed cholesterol-reducing drugs, which were tested in randomized controlled trials (RCTs).

But we have missed a crucial level of knowledge: taxonomic science. The discoveries of basic and population science have no practical value unless they have clinical significance. A clinical trial is of no value if the target disorder has no clinical significance. The identification and control of risk factors could not have got off the ground without an existing body of knowledge of the natural history of ischemic heart disease (IHD). We are all dependent on this great foundation of taxonomic knowledge, most of it gathered over the last two centuries. And it is not a static foundation: it is constantly changing and evolving. The classification of IHD, for example, has evolved in our own time from one based on electrocardiography to one based on angiography.

The laboratory and population sciences can never replace clinical descriptive science. Knowing the innervation of the heart does not tell us the distribution, duration, and quality of anginal pain. Knowing the physiology of digestion does not tell us the pattern of pain in peptic ulcer. We do not know that a biologic deviation from normal is harmful unless we follow people who have the deviation over time. Medical history is full of spurious diseases shown by clinical research to be harmless variants, from sinus arrhythmia and large tonsils to mitral valve prolapse and a tight perineum. The more sensitive our diagnostic technologies, the more risk of spurious "diseases," and the more need for descriptive clinical research.

The history of general practice gives us a good example of the fundamental importance of descriptive taxonomic research. Edward Jenner,[3] a country practitioner, was told by a milkmaid that she could not get smallpox because she had had cowpox. At that time, epidemic smallpox had very high mortality, but if smallpox was transmitted by inoculation to healthy children, the mortality risk was much lower.

With parents facing this agonizing choice, Jenner saw the possibilities in the milkmaid's story. He asked his colleagues to make observations of their own patients, but nothing was confirmed. Instead of giving up as a lesser scientist might have done, Jenner reasoned that what his colleagues were calling cowpox might be a heterogeneous group of infections, only one of which provided immunity to smallpox. So he started to make detailed observations of the skin eruptions of dairy workers. He asked farmers to let him know when an outbreak occurred and eventually, with the help of an artist to draw the lesions, he was confident that he had an accurate description of cowpox and was ready to make his crucial experiment. Even

after publication of his results, critics using vaccine from people wrongly identified as having cowpox tried to discredit his research.

Lack of awareness of the limitations of clinical trials. For logistic, economic, and ethical reasons, the time span of RCTs is limited; 99% of trials last less than 3 years.[4] For chronic diseases, this is not enough time to use significant outcome criteria or to identify the long-term effects of drugs. A by-product of short duration is the use of surrogate markers as outcomes. The early hypertension trials used heart and stroke events as outcomes, but because it is not feasible to do this for every new drug, blood pressure (BP) reduction has been used as a proxy. As recently reported, BP reduction has not proved to be a good surrogate.[5] In his long-term studies of patients with rheumatoid arthritis, Pincus[4] found that the usual surrogates of joint swelling and tenderness were not good predictors of long-term outcomes.

Because trials are so short, they cannot provide much information about the long-term harmful effects of drugs. The new and powerful drugs coming onto the market in increasing numbers will require long-term descriptive studies. For example, between 1960 and 1980, many 1-year drug trials were done on patients with rheumatoid arthritis. Several drugs were equally effective, and textbooks began to give rheumatoid arthritis a good prognosis. Conversely, 10-year descriptive studies by Pincus told a different story.[4] Most of the drugs effective over 1 year were ineffective over the longer term, or were discontinued because of adverse effects. The prognosis over 10 years was much worse than over 1 year.

Randomized controlled trials often use highly selected fractions of the population at risk. The elderly, those with comorbidity, and female patients are often excluded. The noncompliant, the poor, the uneducated, and those who refuse treatment tend not to enrol in RCTs. Even all those who are enrolled might not be randomized. A letter in the *Canadian Medical Association Journal*[6] has drawn attention to the limitations of meta-analysis in this regard. In a descriptive study of one's own patients, each can be followed, and there need be no drop-outs.

Lack of confidence in our own ability to add to knowledge. We tend to underestimate our own practices as a source of knowledge, or we think that all diseases have now been described and that our taxonomic vocabulary is a given rather than an ever-changing and evolving process: a map that is always being made and remade.

That was certainly my own feeling when I started practice. I wanted to do research toward my doctorate but could not think of a single question arising from my practice. In the end, I did a project that had nothing to do with my practice. What made me realize the potential of my own practice as a source of new knowledge was an elderly patient who complained of disabling pain and stiffness in her shoulder and hip girdles. The joints were normal except for stiffness in hips and shoulders; all investigations were negative except for a very high erythrocyte sedimentation rate. The picture did not fit with anything I had seen before. I consulted an experienced internist who was puzzled too. He said "Let's try prednisone," which had just become available. The result was an immediate and striking restoration of function. Seeking more information about this unfamiliar condition, I presented her case at the local medical society, but nobody could help me, nor could the literature.

A few months later, reading an issue of *The Practitioner* on rheumatology, I saw a paragraph headed "Bagratuni's Syndrome." This Italian physician had described several cases just like my patient's. He called it anarthritic rheumatoid arthritis. A few months later came Barber's[7] definitive description and the suggested name "polymyalgia rheumatica." Six years later Bagratuni published a 10-year follow-up of his cases, confirming the relatively benign course of the illness.[8] So I had witnessed the birth of a new disease. Of course it was not new: it was newly described and its description coincided with the introduction of an effective remedy. A new remedy can give us a better taxonomic map. The history of Canadian medicine provides a striking example. The introduction of insulin immediately divided diabetes into its two big categories, insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, which served us very well for almost a century. The introduction of sumatriptan for migraine could do the same for headache.

My experience with polymyalgia rheumatica showed me that original observation could be made in general practice. I started keeping notes on conditions that interested me: early symptoms of cancer, depression, brucellosis in the farming community, coronary heart disease, infectious mononucleosis, and thyroiditis. I found things that were not in the books or that were in the books, but were wrong. None of this was groundbreaking: there were no "breakthroughs," just a few

small contributions to knowledge. Was it worth the effort? I enjoyed doing it, and I did not have to drive myself. There was the occasional joy of discovery, and I learned a lot as a clinician, especially about the early stages of illness.[9]

Devaluation of descriptive taxonomic science. A fourth reason is the devaluation of descriptive, taxonomic research in the medical schools and in biology as a whole. It is as if clinicians cannot be scientists unless they are working in laboratories. A descriptive study can be dismissed with that hackneyed label "anecdotal," however meticulous the observations. No wonder we have a crisis in clinical research.[10]

General practice has four advantages as an environment for clinical research. First, for any disease, we see the whole range, from the mildest cases to the most severe, so we are in a position to give a fuller description than a referral clinic. Some diseases with low referral rates can be studied only in general practice. Second, because of our long-term relationships with patients, we can follow them for long periods and can obtain very complete follow up by using tracing strategies. Third, we are in a position to add important contextual detail. Fourth, because we see the earliest stages of illness, we can describe its whole natural history, including all the circumstances surrounding its onset. Even for such a common condition as chronic daily headache, there are no descriptions of its natural history from its onset onward. As John Ryle[11] wrote, "There is no disease of which a fuller or additional description does not remain to be written; there is no symptom as yet adequately explored."

Godwin has predicted dire consequences for our poor record in research.[12] Among the suggested remedies are more protected time for faculty, so that they can gain respite from the relentless demands of teaching and patient care. Although necessary for any physician who makes a career in grant-funded research, it is not likely to be possible for most faculty members, unless residency training is transferred entirely to community practices. There is also an implicit suggestion that, to do research, one needs to withdraw from practice. Our great exemplars of research in family practice, however, were clinicians who immersed themselves in practice. Clinical studies of the kind I have described are within the reach of any family physician in academic family medicine or full-time practice. This is one kind of research that can be done only by clinicians. And it can be fun!

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