Clinical research: A personal perspective

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Abstract

Research ought to be inculcated as an attitude during the formative years of every health-care professional. The core elements of research are curiosity, observation, reasoning, and experimentation. These suggestions are supported with suitable examples. Medical advisers in the pharmaceutical industry are in a unique position to act as facilitators of such a process. The tools they can use are also suggested.

Keywords: Clinical research core, clinical research facilitators, clinical research tools

INTRODUCTION

In this essay, I wish to develop the theme that clinical research ought to be inculcated as an attitude during the formative years of every health-care professional so that it could grow into a habit and become second nature throughout his career. I further wish to propose that medical advisers in the pharmaceutical industry, who work at the interface of the industry, health-care organizations, medical teaching institutions, and regulatory authorities, have a unique opportunity to be facilitators of clinical research.

DESIDERATA

The core elements of research are curiosity, observation, reasoning, and experimentation. Curiosity focuses attention on a perceived event and transforms it into an observation. Reasoning imparts meaning to the observation, and grooms it into a concept. The experiment tests the correctness or validity of the concept. If the concept is valid, it adds to the existing knowledge; otherwise, it is either modified or discarded. This is how knowledge accrues over time and progress occurs. Therefore, the process needs to be understood and practiced until it becomes a habit.

Some individuals are born with these core capabilities. Others imbibe them from their peers or seniors. However, some need the assistance of mentors or facilitators to acquire and develop these traits. Of course, some may not be inclined to this pursuit, and be content simply to deliver health care by current practice standards. Even then, as they become aware of new discoveries, they would be in a better position to understand, appreciate, and use them if they also know about the method or process by which the discoveries were made. Hence, in any learning experience, it is productive to know not only what but also how.

SOME EXAMPLES

When Gottlieb came across five young gay men with pneumonia due to a rather innocuous microbe, Pneumocystis carinii, he was curious: was their immune system impaired? He reported the cases in the Morbidity and Mortality Weekly Report published by the Centers for Disease Control and Prevention (CDC). The subsequent discovery of acquired immune deficiency syndrome (AIDS) and its cause, the human immunodeficiency virus (HIV), are now history. Later, the pharmaceutical industry discovered many anti-HIV drugs and sponsored their trials in AIDS. However,
Gottlieb’s curiosity, reasoning, and initiative were seminal to the AIDS saga.[1]

Marshall and Warren had noticed spiral organisms, then called Campylobacter (now Helicobacter) pylori, in the gastric mucosa of patients with gastritis or duodenal ulcer. They were curious. Did the organism cause the disease? Would its elimination cure the disease? To test the causal relationship, Marshall first confirmed that he neither gastritis nor H. pylori in his gastric biopsy. Then, he swallowed a culture of the organism, developed gastritis, and recovered the organism from his gastric biopsy. Later, he showed that drugs such as colloidal bismuth citrate and tinidazole, which killed the organism, promoted healing of peptic ulcer, and prevented its recurrence. The understanding and treatment of acid peptic disease was revolutionized.[2]

Himmatrao Bawaskar, a physician working in a small town on the west coast of India, used to see many patients with red scorpion sting. Most of them died. Why and how? What could be done for them? With these questions in mind, he kept records of these patients, studied them, and noticed a pattern of symptoms, signs, and electrocardiogram changes which resembled those of norepinephrine overdosage. He reasoned that red scorpion venom might be causing a massive release of norepinephrine, and if so, its harmful effects could be countered by an alpha blocker. Hence, he tried prazosin, an alpha blocker, in some patients. It mitigated the symptoms and signs, and saved many of the patients. Now, prazosin is accepted treatment for red scorpion sting; the mortality from this poisoning has plummeted. Thus, Bawaskar grappled with a problem relevant to his patients, and found a solution that worked.[3] Today, he is one of a handful of world experts on red scorpion venom poisoning.

Edward Jenner practiced in an era when smallpox outbreaks were common. He had observed that persons who had suffered from cowpox (Vaccinia) in the past rarely contracted smallpox. From this, he reasoned that inducing mild cowpox in healthy persons might protect them from the much more serious smallpox. Therefore, he experimented by collecting the fluid from cowpox blisters and injecting tiny amounts of it into the skin of healthy persons to raise a cowpox blister. This procedure (vaccination) did protect the persons from smallpox during subsequent outbreaks, confirming the validity of Edward Jenner’s concept. Vaccination was born, and it has now rid the world of smallpox. Even without knowing the precise cause of smallpox, Jenner had discovered an effective method of preventing it.[4]

James Lind, a naval doctor, knew that there were six remedies in vogue for scurvy, which affected many sailors on long voyages. These were cider, sea water, vinegar, elixir of vitriol, barley water, and lemon juice. However, which of the remedies did really work? He reasoned that comparing them under similar conditions might provide an answer. Hence, he treated six pairs of sailors on a voyage with the six remedies, and discovered that lemon juice was the only one which really worked. Without knowing the cause or mechanism of scurvy, Lind was able to identify the only remedy that was effective.[5]

These examples illustrate the various kinds of research a curious, observant, reasoning, and enterprising clinician can do, and thus contribute to the progress of medicine.

**SOME FORMATIVE EXPERIENCES**

In the first year of my MBBS course, I had to undergo a one-year course in biostatistics. Our teacher, J. K. Adranvala, Professor of Preventive and Social Medicine, was a student of Bradford Hill. He emphasized that current knowledge of any subject was always in a state of flux. Therefore, he never prescribed any one textbook, and coaxed us to read some articles from medical journals, such as The Practitioner and the British Medical Journal, to find out current or controversial views on some topic. His questions could not be answered straight from a textbook but required our thinking on it. He never expected a set answer to any question but accepted any answer that was well reasoned. His teachings and attitude have been a major influence on me throughout my career.

When I was preparing for my MD examination in 1965, my wife was doing her internship. During one of her home visits, she encountered a family with four children, three of whom seemed to have gargoylism (Hurler’s syndrome). She asked, “Can we confirm the diagnosis by demonstrating a high concentration of chondroitin sulfate in their urine?” A semi-quantitative spot test had been described in literature in which the color developed by a spot of urine sample was compared with the colors developed by spots of chondroitin sulfate solutions of increasing concentrations. However, pure chondroitin sulfate was not available to us. Taking the help of chemists from the Haffkine Institute, we obtained one gram of pure chondroitin sulfate from ox trachea cartilage which we had collected from the local abattoir. We then set up the test and confirmed the diagnosis. I was then working on my dissertation, studying the effect of anabolic steroids and corticosteroids on the exudative and proliferative components of inflammation. An article I came across had reported that anabolic steroids reduced the loss of chondroitin sulfate from bone matrix. Could they be useful in these children with gargoylism? With the parent’s permission and samples donated by a pharmaceutical company, we treated the children with
nandrolone decanoate for 6 weeks. To our delight, their urine chondroitin sulfate fell, corneal opacities diminished, speech improved, and liver size decreased. We reported the study in the Journal of the J. J. Group of Hospitals,\(^6\) which was later referred to in Kochakian's monograph.\(^7\) As the family left Mumbai, we could not follow the patients further, but the joy of conceiving and testing an idea had a refreshing effect on us.

After I joined the pharmaceutical industry in 1966, I always asked myself what a medical pharmacologist could do better than a nonmedical pharmacologist. The answer was that he could be more perceptive, effective, and useful in a clinical setting rather than in a laboratory. As I had to travel a lot, both within and outside the country, and work at the interface of industry scientists, academic scientists, regulatory authorities, and clinicians, I tried to sustain my academic and clinical interests by participating in teaching or training activities, and supporting or assisting research-inclined clinicians I met.

**SOME INDUSTRIAL EXPERIENCES**

I observed that many doctors whom I met for my clinical trials work had some independent ideas of their own, and these could be accommodated either within the proposed plan or as an independent academic project.

In the late 1960s, I was working with hormonal oral contraceptives containing an estrogen and a progestogen. At that time, similar products containing higher doses of the hormones were in vogue for treating dysfunctional uterine bleeding (DUB). One gynecologist I met asked, "If the idea of treating DUB with hormones is to induce and maintain a state of pseudopregnancy, hoping the pituitary-ovarian relationship will normalize during the period of suspended ovulation, then low-dose oral contraceptives should work as well as the high-dose combinations." I thought this made sense and suggested that he and some more gynecologists who thought similarly, treat ten patients each for a year, record the results, and pool them for analysis. They did and found that over 90% of the patients responded successfully. This helped the doctors change their own practice, and probably that of some others too.

When I was organizing the trials of tinidazole in giardiasis, one gastroenterologist asked whether clearing the parasites would restore gut transit time. I thought this would be a good way to measure functional improvement. We found in literature a method described to measure gut transit time using radio-opaque pellets. After asking a patient to swallow them, the time for their elimination was measured by taking serial X-ray pictures. I obtained these pellets during one of my trips to the UK and passed them on to the gastroenterologist. Using them, he found that the drug not only eliminated the parasites and relieved the symptoms but also normalized gut transit time.\(^8\)

When working on prazosin, an alpha blocker, I met a cardiologist who had learnt a method of assessing left ventricular function, called apexcardiography, which he wanted to use for assessing the effect of prazosin in the patients with heart failure. Digitalis was then the mainstay of treating heart failure, and the use of alpha blockers to reduce afterload was a new concept under trial. I thought this was a good opportunity to study the effect of prazosin, both by itself and with digoxin, employing a factorial design.\(^9\)

When we wanted to introduce an oral single-dose anthelmintic for intestinal worms, my marketing colleagues were feeling diffident as the drug had no effect on whipworms. However, nobody seemed to know whether whipworm was a problem in the country. This was a stimulus to plan a countrywide survey for the prevalence of intestinal nematodes with the help of clinical pathologists. It revealed that except in three small pockets, whipworm infection was not a health problem in the country. This provided an opportunity not only to overcome the diffidence of marketing colleagues but also to do a large prevalence survey based on stratified random sampling. We presented our findings at the annual gastroenterology meeting that year and later published them.\(^10\)

The midline incision used for total knee replacement surgery often causes numbness of the lateral flap after the operation. An orthopedic surgeon believed that a lateral incision would avoid this, and wanted to compare the outcome of the two incisions in patients selected for bilateral operation, using a midline incision on one side and a lateral incision on the other. I helped him plan a study using Wald's sequential analysis, based on the patient's preferences, which revealed that in the short term the lateral incision was indeed better than the midline incision. The verdict was out by the time the 11th patient was evaluated.

**RESEARCH FACILITATORS**

The experiences described above have convinced me that medical advisers working in the pharmaceutical industry are in a unique position to act as facilitators of clinical research in the area of their operation if they adopt this role and their organizations let them do it as a corporate social responsibility. Apart from motivating and empowering individual clinicians, they can help develop networks of clinicians interested in specific clinical or therapeutic areas, and thus encourage cooperative, collaborative, and relevant research, both short and long term. They can extend this service even to postgraduate students during their formative years. For this enterprise, they will need a tool for theoretical foundation and a tool for
collection, management, and analysis of data. Fortunately, such tools are readily available. I shall describe two that I have used and found effective.

**THE UNION BOOKLET**

The Union (formerly International Union Against Tuberculosis and Lung Diseases) has published a book titled *Research Methods for Promotion of Lung Health*. It can be freely downloaded from the Union website. The title is a bit distracting because, except for the first ten pages of the first chapter, which talks about lung health, the rest of the booklet is an extremely well-written primer of clinical research. It deals with both the conceptual and the practical aspects of clinical research: framing of a question or a hypothesis, selection of subjects and sample size, study design, choice of variables, protocol writing, data collection, data management, data analysis, data interpretation, and report writing. Besides, it illustrates the use of the second tool described below, Epi Info (Centers for Disease Control and Prevention, Atlanta, Georgia, USA), for designing forms, collecting data, and analyzing them. I have always wondered why this booklet has not been widely used.

**EPI INFO**

This is a free computer program downloadable from the website of the CDC. It is a combination of two programs: a relational database system, built on Microsoft Access, and a statistical program for descriptive and analytical statistics. Besides, it provides a link to another free statistical program OpenEpi (www.openepi.com) that performs some additional procedures.

The current version of Epi Info is 7.2, which comes in two forms: One for installation on a computer, and one for saving on and running from a pen drive. The second form is useful where the researcher has no right to install the program on the computer he is using. The CDC website also maintains and provides older versions of Epi Info for those who are used to them or prefer them.

One can easily learn Epi Info from the User Guide available on the website, and from 54 video tutorials available on YouTube. Besides, one can have questions answered or problems solved by the Epi Info team.

For field work, Epi Info forms can be loaded on mobile devices for data collection.

**SUMMARY**

I have tried to make out a case that research ought to be inculcated as an attitude during the formative years of every health-care professional so that it could grow into a habit and become second nature throughout his career. I believe medical advisers in the pharmaceutical industry are in a unique position to act as facilitators of such a process. If they do, they will embellish their career with a purpose, help the industry to meet one of its social responsibilities, and contribute to the progress of medicine.

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There are no conflicts of interest.

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