Commentary

# The Hitchhiker's Guide to Research in Clinical Biochemistry

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**Introduction**

Research within Clinical Biochemistry is at a crossroads. There is currently a degree of navel gazing about what the future academic direction for our profession should be. However, our speciality is distinctive in many ways: it occupies a unique position in medicine at the interface between laboratory testing and clinical diagnosis; we have a closer understanding of the concepts and limitations of diagnostic testing than most others in medicine; we have a history of being at the forefront of using information technology within healthcare; we are also probably a self-selected group whose abilities include being able to rigorously evaluate complex sets of data and then to draw conclusions.

Taken together, these talents mean our discipline should be integral to the development of 'evidence-based' medicine and be central in converting research findings into clinical practice, as is now called 'translational research'. With some lateral thinking we can also help answer some of the fundamental questions related to Clinical Biochemistry and within the many specialities with whom we liaise.

This article gives a personal view of how anyone, whether in an academic centre or not, can make valuable research contributions to Clinical Biochemistry without having to assume they need large funding beforehand. Rather, they just need an inquisitive mind and an enjoyment of the speciality. A number of examples are given of my own experience, but the intention is just to be illustrative rather than to bolster my ego or my number of citations.

**Why Do Research?**

We are often told that research is a central part of our jobs, as it is for any healthcare professional, without usually understanding why or how it can possibly be achieved. The author of this article has certainly not always been enamoured with the thought of doing research. As a medical student, I could not understand why someone would wish to devote so much time to get, at best, a single line in a textbook written about their work.

But I was missing the point. To be the first human to have thought of an idea, no matter how unimportant, and have found a way of answering a research question is very satisfying personally. Indeed the satisfaction is often completely disproportionate to the achievement made. In addition, any employing institution is also likely to be pleased by the profile given to the organisation. However, beyond self-satisfaction, we need to remember that the main purpose of the research is that we may actually report on something which will help - either directly or indirectly - the patients that we look after.

When applying for my first posts I used to wonder, with my medical student scepticism, why research seemed to be such an important part of a curriculum vitae. Should doing your current job, and doing it well, I thought, not be sufficient on its own? Having sat on the other side of the interview table several times I have finally been able to answer my own question. A research record is one way of marking someone out as being able to develop ideas, to formulate these ideas into plans and to be able to express their thoughts clearly. It means they are likely to be a good communicator (in writing, at least), a finisher of tasks and probably a good teamworker. Also, since research can seldom be done solely during working hours, and assuming they are not deficient in their day job, it also distinguishes them as someone who probably works harder than most. Lastly, as we would all wish to have colleagues we know we can work with, a research record just might indicate that the candidate is a likeminded person.

Of course, all these qualities can be demonstrated in ways other than through research, but I think I now understand why achievement in this area was as valued as it was.

**Rules of Research**

If research can be satisfying, important and probably only of help in career progression then it follows that there should be equal exposure to it. However, not everyone works in a centre of academic excellence where there is a culture of research, so it is not always obvious how to even start to be involved.

In this case I would recommend following what I've modestly called 'Kilpatrick's Seven Rules of Research' (Table). The following gives some examples of how some of these 'rules' can be put into practice.

**Table.** Kilpatrick's Seven Rules of Research.

- Don't be afraid of asking daft questions
- Don't assume someone has already studied it
- If the question makes you curious, the chances are other people will also want to know the answer too
- If the study looks difficult, try to think laterally
- Jump on unusual findings or promising leads
- Some of the most interesting studies are cheap to perform
- Get it published

***Don't be Afraid of Asking Daft Questions***

Simply because they are probably not daft after all. 'Daft' questions are also often the ones that vex people who are even specialists in that area of the laboratory. When I first started to develop an interest in diabetes, the glucose test strip market was beginning to burgeon with glucose oxidase-based meters. I asked the simple question 'where does the oxygen come from?', by which I meant, did the enzyme use oxygen from the atmosphere or from the blood sample itself? Trying to think laterally, there then followed plenty of tinkering with rubber tubing to connect a Boyle's anaesthetic machine to a tonometer in order to be able to dial up a desired $pO_2$ and $pCO_2$ in a blood sample. We established that some contemporary tests strips obviously used sample rather than atmospheric oxygen and so could give inaccurate results in hypoxic patients or in those on oxygen treatment.[1]

***Don't Assume Someone has Already Studied It***

When training, it is easy to assume that all the research questions worth answering have already been done so, or that solving the difficult ones will be impossible without large grants. The further along the career you travel, the more obvious it becomes that many of the fundamental issues in a medical subspeciality have still to be addressed. A simple example of my own followed on from the glucose meter experiments. I asked how we knew whether a whole blood sample for point-of-care-testing instruments was haemolysed or not. As it transpired, no one had ever looked at this, even though in retrospect it should probably have been one of the first questions asked of these systems. So by deliberately haemolysing blood to various extents with a sonicator, we showed that this could be a significant source of error for some glucose meter systems.[2]

***Jump on Unusual Findings***

Many a discovery and career has been made either because of sheer luck or because the potential of an observation has been realised by someone but not others. Such events are unpredictable and infrequent, but when they do happen it is important not to let a busy routine job mean that they are never followed up. Such a moment happened when assessing the renal function of patients with hypo- and hyperthyroidism before and after treatment. Creatinine concentrations were high in hypothyroidism, low in hyperthyroidism and both normalised on treatment. There was still a lingering doubt that the creatinine may not be giving an accurate indication of glomerular filtration rate (GFR), so the samples were sent to another laboratory to measure cystatin C which, at that time, was a marker of GFR with apparently few, if any, limitations.[3] The results suggested the samples had been transposed as the cystatin C was, in fact, high in hyperthyroidism and low in hypothyroidism. Tempting though it was to just accept the transposition and not ask the laboratory to rerun the samples - especially as they had been done as a favour - there was the realisation that hyperthyroidism was possibly leading to an overproduction of cystatin C and vice versa with hypothyroidism. This ultimately proved to be the case and was reported as the first major limitation of cystatin C to be found.[4]

***Armchair Research***

This expression was coined by a colleague to describe my appetite for interrogating large databases to try to answer some basic questions related to Clinical Biochemistry, and to perhaps debunk conventional wisdom along the way. We have, at our disposal, a wealth of data recorded in our laboratory computers just waiting to be examined. Take the simple question of whether hypothyroidism is associated with hyponatraemia. Of course it is, because we have often been told so,[5] but on closer inspection the evidence for this strays little from simple case reports. Some data had disputed the relationship, but also had its limitations.[6] From our laboratory database, we were able to identify 999 patients who were newly diagnosed with hypothyroidism by their family doctors (so presumably were not also acutely unwell) and found that the concurrently measured serum sodium distribution was virtually identical to the distribution in euthyroid patients.[7] It seems, therefore, that any association is unlikely to be causal.

If our laboratory data can be somehow linked with other databases then they can become even more powerful tools. We already know that as estimated GFR (eGFR) falls from normal values, mortality increases.[8] By linking to the register of deaths in our population, we were able to determine that patients with high eGFR (>90 mL/min/1.73m$^2$) are also at higher risk than the 'sweet-spot' of 60–89 mL/min/1.73m$^2$, such that the distribution is actually 'U' shaped.[9] Sticking with eGFR, an

ongoing debate in the UK is whether urea measurement is of any value now that we report this calculation. Most people assume that urea gives additional evidence of hydration, but there is little data to support this. However, we were able to link admission urea and creatinine measurements with the urine specific gravity of patients recorded by automated urine analysers in our Accident and Emergency (A&E). It showed that urea measurement did add to creatinine in predicting this urine marker of hydration, albeit not especially strongly.[10]

*Medical Freakonomics*

'Freakonomics' is the title of a book written by the US economist Steven Levitt. He too has asked unusual questions of large datasets, but has also examined how human nature can impact on the business economy.[11] As a laboratory speciality, we are in a strong position to be able to determine how human nature can impact on our health economy.

When we moved to having ward terminals to access results in wards, we stopped telephoning abnormal results to those clinical areas in the knowledge they would have them available to look at. Human nature said to me that if I worked on these wards and had the choice of having a coffee or looking at laboratory results, I would be tempted by the coffee. Sure enough, we found that not only was there a delay between the time results became available and being accessed, but nearly half of A&E results were never viewed, including a significant number which were likely to have led to an immediate change in patient management.[12] We now telephone very abnormal results again.

It is already known that women have a poorer outcome than men post myocardial infarction (MI), and this is at least partly due to the fact that they appear to be less aggressively treated with lipid lowering or other drugs and fewer undergo cardiac rehabilitation. We linked our troponin measurements to the discharge diagnosis database for our hospital and found, not surprisingly, that as troponin concentrations increased the chances of being discharged with a myocardial infarction diagnosis increased as well. What was less predictable was that, on average, a man was 50% more likely to go home with that diagnosis than a women with the same troponin level.[13] Human nature seemed to be making the clinician act differently depending on gender, and so in addition to being managed less well post MI, women seemed to be at less chance of being diagnosed with an MI in the first place.

*Other Databases*

If your own laboratory system does not satisfy your wishes there may be another database that does. The Diabetes Control and Complications Trial was the seminal study in type 1 diabetes that showed for the first time that improving glycaemic control could reduce the risk of developing the microvascular complications of the disease. This database was made public in 2003 and has since allowed independent investigators, such as ourselves, to help address questions which the original study never envisaged answering. These have ranged from showing that increased glucose variability does not seem to influence the risk of developing microvascular complications,[14] to more eccentric observations demonstrating that tall patients develop neuropathy before small ones. Many other datasets have been made publicly available and could well prove to be relevant to Clinical Biochemistry, such as those of the National Institute of Diabetes and Digestive and Kidney Diseases.[15]

***Get It Published***

Standing by your first poster presentation at a national meeting is a proud moment for every researcher. However, for the work to get its widest (and usually deserved) dissemination, it is important that every effort is put towards publishing the article. Despite this, only a minority of abstracts at meetings make it to full publication.[16]

Guaranteeing a larger audience is not the only reason for writing up an article for publication. A salutary lesson involved the cystatin C study already described above. This serendipitous finding, 17 years after the initial paper proposing its use as a marker of GFR,[17] was presented as a poster at the Association for Clinical Biochemistry meeting in the UK in 2002 and published in April of the following year.[4] Within six months, three further groups independently reported the same finding.[18-20] Needless to say, it would have been disheartening if their publications had been the first to break the news. Moreover, being the fourth, rather than the first, would have meant it was far more difficult for the paper to be accepted for publication at all.

**Issues Presenting Barriers to Research**

***Fear of the Unknown***

There is now a plethora of regulations related to research governance, and knowing how to comply with these is no easy task for inexperienced non-academics. It may be, in the UK at least, that the project does not need to undergo a full Research Ethics Committee submission if it is being done as part of a clinical audit. This is defined as an analysis where care is being assessed against clearly defined standards. Since, for example, it is recommended that patients with raised cardiac troponin concentrations be diagnosed as having had a myocardial infarction, it was appropriate that the troponin study mentioned earlier be an audit of local practice, even though it ultimately unearthed the differences between genders. Approval for a clinical audit can usually be obtained from the local hospital in a manner that is much less involved than that required for a full research study.

For other projects, ethical approval will undoubtedly be required. Having someone to help with this who has previously gone through the process is invaluable. There is no particular need for them to be laboratory-based and they may well be employed within the Research and Development infrastructure of the hospital. As might be expected, having done the submission once, subsequent applications are much more straightforward. Indeed, that person should be expected (or even compelled) to help others with their own proposals. My own experience is that the types of studies I am recommending, by not involving drugs or patient intervention, seldom give rise to ethical committee concerns beyond maintaining patient confidentiality. However, the submission can lead to a delay of 2–3 months in starting the study.

***Time and Other Resources***

These seem to be in increasingly short supply in clinical laboratories throughout the world and this is especially true when it comes to prioritising research. However, it is not a coincidence that the words 'Research' and 'Development' are often used together since the laboratories at the forefront of the former tend also to those at the forefront of implementing new technologies, reconfiguring services and being respected (and therefore supported) by clinical colleagues. Having a research ethic in a department may make further financial sense as the interest it engenders often promotes the recruitment and retention of the most talented staff. Having mentors to help direct and advise junior staff is also important in order to make sure the culture is not the sole preserve of senior staff members.

**Conclusions**

Being able to conduct research is one reason why many of us chose Clinical Biochemistry as a career, but in recent years, for various reasons, it has become more difficult for this source of job satisfaction to be accommodated. I hope this article has shown that large grant application success is not always required to perform meaningful research in our speciality. Although the approach described could be accused of being simplistic and naïve, I feel that this is still one way in which our discipline can continue to make a unique and relevant contribution to healthcare research.

**Competing Interests**: None declared.

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