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SPECIAL ARTICLE

Clinical research

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An invitation to provide information on clinical research which will help those embarking on a career in academic medicine implies that the author is an experienced authority in this field, that creativity can be taught, and that the author can teach. Since my only virtue is that I have been involved in research for a quarter of a century and there is a reasonable chance that I am older than those who might read this 'advice', I have decided to produce this manuscript in the form of 'a message to a young researcher'.

About research

Welcome, young researcher, to a bipolar world where dreams are encouraged, where novel ideas are highly prized, where the ability to admit to ignorance is a valuable attribute and where the depression induced by interminable hard and often repetitive work occasionally gives way to a great but usually transient feeling of elation. Welcome to a world which, after a quarter of a century, I still consider to be filled with wonder, the world of research.

Research and academic medicine

Before you flee in terror, protesting that you only want to care for your patients and teach your students, let me hasten to convince you that you 'cannot reach fulfilment as a full-time member of a medical faculty unless you are involved in research'.[1] This argument is not new. It is almost 100 years since Sir William Osler pointed out that 'the practice of medicine is an art based on science'. Sir William suggested that medical schools should employ persons 'who have, first, enthusiasm, that deep love of a subject and desire to teach and extend it without which all instruction becomes cold and lifeless; secondly, a full and personal knowledge of the branch taught: not second-hand information derived from books but the living experience derived from experimental and practical work done in the best laboratories'.[2]

I have previously argued that the components of academic medicine, teaching, research and patient care are part of a single function and not distinct entities.[3] Separation of this function is analogous to the colours produced when white light is passed through a prism. However, when the process is reversed and viewed holistically, perturbation of any component will affect the resultant blend. Thus any alteration in the nature or relative proportion of teaching, research and patient care will influence academic medicine in its entirety. I would now argue that only those who are or have been engaged in good research, basic or applied, will have developed that critical facility vital for excellent patient care and for teaching. It is thus essential that every member of the professional staff of an academic complex should be actively engaged in research and that this involvement should start at an early stage of their training.

The scope of clinical research

There is a considerable lack of clarity about the scope and definition of clinical research. Comroe and Dripps,[4] in a landmark paper entitled 'Scientific basis for the support of biomedical science', attempted to separate clinical and non-clinical research in order to determine the contribution of each to major clinical advances in cardiovascular and pulmonary disease. After considerable thought and consultation they defined research as clinically orientated 'even if it was performed entirely on animals, tissues, cells or subcellular particles, if the author mentions, even briefly, an interest in diagnosis, treatment, or prevention of a clinical disorder'. Research was not clinically orientated if the authors 'neither state nor suggest any direct or indirect bearing that their research might have on a clinical disorder of humans'. Finally, research was considered to be basic 'when the investigator, in addition to observing, describing, or measuring, attempts to determine the mechanisms responsible for the observed effects. Thus clinical research may be applied or basic or both.

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Unshackling the mind (curiosity will not kill the cat!)

Having decided that you should enter the world of research, young researcher, it is important that you should rid yourself of many of the attitudes which you have acquired during your school and university years, since the most fundamental requirement for any type of research is to achieve a state of uninhibited curiosity which will allow you to formulate a hypothesis. This is particularly difficult for graduates in medicine who have most often been force-fed a diet of facts by a succession of authoritarian, and expert, teachers. This didactic teaching is usually accompanied by a system of evaluation in which 'professing ignorance' is akin to committing suicide and a culture in which admitting mistakes is frowned upon. You will have to find the courage to enter a new mind-set since, as Karl Popper reminds us, 'with each step forward, with each problem which we solve, we not only discover new and unsolved problems, but we also discover that where we believed that we were standing on firm and safe ground, all things were in truth insecure and in a state of flux'.[5] Indeed 'the staggering progress of the natural sciences constantly opens our eyes anew to our ignorance'.[5]

You will need to be re-educated, young researcher, so that you can accept George Bernard Shaw's dictum that 'All great truths begin as blasphemies'[6] and 'the golden rule is that there are no golden rules'.[7] Albert Einstein exemplified this notion by daring to suggest that space itself can be distorted by matter. You should bear in mind that Sir William Osler, in describing a man whom he admired, said 'Sydenham was called "a man of many doubts" and therein lay the secret of his great strength'.[8] You should consider David Miller's injunction, 'If we are in earnest to discover what the world is like, we must be prepared to correct mistakes; but if we are to correct them, we must be fully prepared to make them first. In the realm of errors cure is more important than prevention. Indeed, the world into which the young investigator enters has no truths only hypotheses which have as yet not been disproved.'[5]

Formulating a hypothesis

While science is usually thought of as being both disciplined and logical, formulation of a hypothesis may be inhibited by both of these processes. In his book, *Induction and Intuition in Scientific Thought*, Sir Peter Medawar states: 'Science in its forward motion is not logically propelled. Scientific reasoning is an exploratory dialogue that can always be resolved into two voices or two episodes of thought: imaginative and critical, which alternate and interact. In the imaginative episode we form an opinion, take a view, make an informed guess, which might explain the phenomena under investigation. The generative act is the formation of the hypothesis: "We must entertain some hypothesis" said Pierce, "or else forego all further knowledge:", for hypothetical reason "is the only kind of argument which starts a new idea".[9] Stuart Saunders points out that the process by which we come to formulate a hypothesis is not illogical but non-logical, that is, outside logic, but once we have formed an opinion we can expose it to criticism, usually by experimentation.[1] Jaques Barzun reminds us that criticism differs entirely from attack or complaint. Criticism, he states, demands action.[10]

Conquering Everest: one step at a time

It is fashionable in some circles, young scientist, to denigrate basic research. Terms such as 'blue-sky research' are often used to denote irrelevant, 'curiosity-driven' research by those who forget that Wilhelm Roentgen was studying how rays travelled in a vacuum when he discovered X-rays. Meteorologists of course may conduct highly relevant applied research on blue-skies and applied research, such as that performed by Louis Pasteur, who was employed by the French Government to keep wine from turning into vinegar, gave rise to the discipline of microbiology. Thus, both curiosity and need may lead to great research and you should be more concerned with the quality of the hypothesis to be tested than by whether it is basic or applied. Finally, the generation of good research ideas improves with practice. You should while seeing patients, attending lectures, reading articles or bathing (cf. Archimedes), constantly attempt to generate hypotheses or to ask yourself how you can extend knowledge. Some of these ideas will prove to be worth testing.

Before turning to such action it is well to note the advice of Nobel Laureate Arthur Kornberg who, in addressing the type of question that researchers should aim to answer, stated: 'It is the essence of scientific discipline to ask small, humble and answerable questions. Instead of reaching for the whole truth the scientist examines small, defined, and clearly separable phenomena. The pattern of science is a stepwise progression of what came before. Whereas the doctor must treat the whole patient and at once the scientist can isolate the smallest facet that intrigues him and grapple with it for as long as it takes' . . . and 'the clinical investigator should ask a small and modest question, and focus on it in a laser-beam fashion and then maintain that focus until the beam burns through'.[11]

Choosing a mentor

Most successful once-young researchers speak with fondness of their mentors. Unlike parents, mentors can be chosen and it is my firm conviction that this should be done with great care. A potential mentor's success in research should be defined not only in terms of the numbers of papers published and how often these have been quoted by others but by the quality of research of the young scientists who have passed through his hands. Truly great mentors encourage their protégés to surpass them.

Scientific discipline

Having generated the hypothesis, young researcher, you will rapidly be reminded that research is 1% inspiration and 99% perspiration. Testing the hypothesis demands both discipline and a logical and focused approach. This must start with a thorough and in depth knowledge of the relevant literature. Once again your undergraduate programme, which consisted of a series of single and often superficial exposures to various disciplines, may not have prepared you for this task. The transition from reading textbooks or review journals to the detailed study of scientific journals is not easy and in this you may need guidance. However, it is vital, young researcher, that by the end of the process you should know more about your specific subject than any of your mentors.

Acquisition of skills

There are two schools of thought regarding the acquisition of the skills necessary to do research. Computer literacy, and understanding of elementary statistics, laboratory techniques, etc., can be acquired either by attending formal courses or by use. My personal bias is towards the latter. I believe that the need to know is one of the most powerful motivating forces for learning. Furthermore, the shorter the delay between acquisition and application of knowledge and skills, the greater their retention. It is vital that you should both understand the methods used in your study and be competent in performing those tests.

Study design

Next, young researcher, you will need to design your study and this should be committed to paper as a formal protocol. It is useful to consult a competent statistician at this stage. Winifred Castle, a British statistician, once wrote: 'We researchers use statistics the way a drunkard uses a lamp post, more for support than illumination.'[12] Statistical methods cannot compensate for bias due to poor study design, low response rate or high drop-out rates. A statistician may spot problems in design and can estimate the number of observations required, provided that you can predict the approximate size of change expected and the level of confidence required. In the absence of any specific adverse effects the anticipated drop-out rate can be gleaned from other workers in the same field and the numbers can be adjusted accordingly.

It is worthwhile remembering, young researcher, that the probability or '*P*' value is only a statement of the likelihood that the observed difference could be due to chance. In clinical research the size of the difference must also be considered. Very small differences in outcome, if real, will be significant when the numbers of observations are large while large differences may fail to reach significance if the number of observations is too small.[13]

I have already pointed out that clinical research extends well beyond studies involving the effects of an agent, an intervention or a form of treatment. Since these studies are common it is appropriate to mention the various designs and their strengths and weaknesses briefly.[13,14] (*a*) The strongest of these is the *double-blind randomised control trial* (RCT). In these studies subjects are randomly allocated to two or more groups each receiving a different treatment. Neither the patient nor the observer knows which treatment the patient has received until the study has been completed. Strengths include the fact that the study is prospective, the unlikelihood that the groups will be dissimilar and a lack of observer bias. Weaknesses include the cost (if numbers are large) the study period (which is often long) and the small but real possibility that volunteers might differ from persons declining randomisation. (*b*) In the *cohort study* two groups are selected; one of them has, for various reasons, been exposed to the agent and the other not. This type of study is considerably cheaper than RCTs but the study is also much less powerful in testing a hypothesis. The study period is usually shorter and the fact that persons selected have already been exposed to the 'agent' releases the researcher from any ethical dilemma that might have occurred in a randomised study. However, the groups may be different, unexposed controls may be hard to find and the study is not blinded and may thus be biased. (*c*) *Prospective surveys* are similar to cohort studies but here only one large group is selected. With time, some will be exposed to the agent and others not. The outcome is usually assessed at a defined period in time. The advantages and disadvantages are similar to those of the cohort study but in addition the prospective survey suffers from the potential disadvantage that the numbers in the exposed group may turn out to be too small. (*d*) In *case control studies* (syn. retrospective studies) a group who already have the outcome are compared to a group who have not. A history of all possible exposures is then obtained. This is useful where the outcome is rare (e.g. cases being followed in a specialist clinic) or delayed, but the retrospective design does not allow the exclusion of other agents which might account for the outcome. (*e*) In *cross-sectional surveys* groups are interviewed or examined at a single point in time to determine whether or not they have been 'exposed' or have an outcome. The main advantage here is that exposure is not intentional; however, it is a weak method and subject to confusion between cause and effect. Finally, (*f*) in *'before and after' studies*, the outcome is assessed before and after intervention or exposure. While cheap and easy to do these studies are weak since the outcome may be attributable to another factor.

Extending the study

One of the most important attributes of any scientist is the ability to notice and to follow any interesting lead which may present itself during the course of a study. This is best illustrated by Fleming's discovery of penicillin. Do not be afraid to follow such leads.

Preparing the manuscript

The final phase in any study is the preparation of a manuscript and its submission for publication. Here it is well to heed the advice 'when all else fails read the instructions'. Most journals provide precise instructions to authors and these should be strictly adhered to. It is extremely useful to read several papers in the journal to which you have decided to submit your article in order to acquaint yourself with its style. Short papers with an informative abstract, an interesting introduction, precise methods, clear results and a disciplined and relevant discussion are best. Short, familiar words should be used and esoteric jargon avoided. Tables and figures save hundreds of words and are appreciated by most readers. References should be kept to a minimum.

Research and the new South Africa

I have already suggested that you should be more concerned about the quality of your research project than whether it is basic or applied. However, lest I am accused of dodging the issue let me comment on the research which I would favour in 'the new South Africa'. In doing so I will attempt to support my personal prejudices with examples (remember that there are examples to support other prejudices). I believe that basic research will continue to provide the vast majority of the major advances in health in the years to come. Comroe and Dripps[4] found that of all work judged to be essential or crucial for later major clinical advances in cardiovascular and pulmonary disease, 61,7% was 'basic'. I would use the more modern example of AIDS in Africa to argue that their finding is universally applicable. Were it not for basic science we would be dealing with a condition characterised by fever, wasting, cough and in some instances neurological and other system abnormalities. In adults the condition may appear to relate to promiscuity and to previous transfusion (although this would not be proved without basic science). Basic science has resulted in identification of the HIV, knowledge of the immune system and its abnormality, the nature of secondary infections, etc. Basic science will also provide the vaccine and the antiviral agent which will eradicate or cure this disease.

It has been suggested that South Africa, with its relatively limited resources, should concentrate on community-based epidemiological research and allow wealthier countries to solve the problems identified. This is a dangerous proposition devoid of foresight. Basic research devoted to diseases common in Africa enjoys a low priority in developed countries. As clinical researchers we should assist our colleagues in epidemiology to identify the problems which we face in our region and apply our minds and basic science techniques to solving them. I am convinced that such basic research should remain a major priority in South Africa and that funding and training in this area should increase rather than decrease in the years to come.

Finally, since funds and available expertise are in short supply, we should build on excellence. We simply cannot afford bad research. Centres of excellence should be maintained as a priority and within these training posts, young researchers should enjoy the highest priority, with guaranteed funding. In time the expertise will spill out to new centres and the culture of research will spread to those departments in which it was previously lacking. Our universities should commit themselves to research by promoting successful researchers and by appointing persons with proven track records in this sphere to chairs in academic departments.

The joy of research

I have said little about the joy of the research. Seeing your completed work in print or, better still, quoted in someone else's paper evokes a feeling which is difficult to describe. Hopefully, by then, young researcher, you will be involved in another study and the resultant pain will prevent you from developing a swollen head.

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