VIEWPOINT

Research

Juggling Career Aspirations with Quality and Relevance to the Caribbean

N Kissoon

It is a pleasure and honour to be invited to give a keynote address which incidentally coincides with the twenty-fifth anniversary of my graduation. I feel a bit disingenuous standing here because in the audience I see mentors and colleagues who are better qualified to grapple with the complex issue of career aspirations and quality and relevance in research. We stand at a very critical time in the history of the Faculty of Medical Sciences, The University of the West Indies. I am pleased to see that many of you have recognized this and have designated the important issue of "Research and Caribbean Healthcare" as the theme for this conference. Research advances to benefit regional health is one of the reasons the Medical Faculty of The University of the West Indies exists. The chairman of this Medical Alumni Association got it right when he stated, "While research is expected to influence regional, national and institutional healthcare initiatives, in the final analysis it is translated to the benefit of patients at the practitioner level." In the allotted time, I will attempt to address the importance of research, why we do research, what is good research and some issues that would be relevant to those of you who work exclusively in the Caribbean.

Well, why is research endeavours important for the Caribbean? For the past decade, it has been well recognized that a global inequity in research, efforts dubbed the 10/90 gap exists. This term refers to the fact that less than 10% of the estimated US $70 billion spent annually on health research addresses the conditions that account for 90% of the burden of disease worldwide, as measured by the number of disability-adjusted-life years (1). The implication is that the health of the poor, particularly in developing countries such as the Caribbean, has not been adequately addressed by the sponsors of health research. Recognition of this fact has led to a Global Forum for Health Research based at the World Health Organization. This was created in 1997 to work toward the reduction of the 10/90 gap, although so far progress has been slow (2). It is the poor in society who bear the disproportionate burden of ill health. Therefore some interventions may have relatively greater benefit to those societies. There is no doubt that relevant research done meticulously will be rewarding for researchers. However, more importantly, if the findings are translated into societal policies for healthcare delivery, they will likely lead to improvement of the overall health of our society.

Many of us in this room are involved in conducting medical research. One of the first questions we need to address is why do we do research. Anderson in the Lancet in 1986 spoke about the "YUMMPIES" or young upwardly mobile medical professionals. Many of us can identify colleagues who certainly fit this description; those who feel the yardstick for success in their careers will be their publication record. However, there are more compelling reasons to conduct research. These are summarized very elegantly by Kramer a few years ago (Fig) (3). In his opinion, the lowest goal for medical research is improving one's *curriculum vitae*, which would likely fit into the group of the YUMMPIES. Many are caught on this treadmill

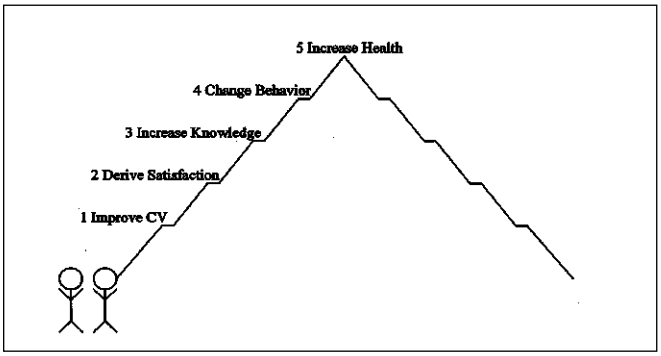

Figure: The Mount Purgatory of medical research*

* Adapted from Kramer MS (3)

because of the 'publish or perish' attitude that exists in many universities. This is likely to lead to poor research and is certainly research done for the wrong reason. It is my opinion that not everyone in university departments should be expected to do research. Research for the sake of research will lead to work of dubious quality and indeed may lead not only to erroneous but possibly dangerous results.

The second reason for doing research is level two, which is to derive personal satisfaction. Personal satisfaction is what we all seek to derive in our everyday lives and jobs, and it may indeed be easier to recruit individuals if the activity were satisfying personally. Personal satisfaction in and of itself is not enough to justify the time, effort, and

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money spent in research. A better reason (Level 3) is to increase the level of knowledge. Kramer's opinion, to which I concur, is that while increasing knowledge may indeed be true to some extent (although not entirely true) for mathematics and theoretical physics, we cannot justify taxpayers money and the large expenditures for medical research for the goal of increasing knowledge. In fact, one can argue that even in mathematics and theoretical physics the long-term goal is to lead to useful technology, some which we take for granted in our everyday existence.

A more worthy goal is level four, which is the expectation that research will change other researchers behaviour. This may allow others to conduct their research in an ethical and rigorous manner. However, by and of itself, it will not be of any benefit to society if the questions posed are not relevant, if they are not pursued in a rigorous manner and if the findings are not acted upon and "translated to the benefit of patients at the practitioner level".

Finally, the ultimate goal of research should be improving health of the target population. While this goal may not always be achieved, if we do not aim at improved health, we certainly will never get there. There are many different facets in improving the health of a society, which is a topic for another day. However, judging from my conversations with many of you, it seems that a good starting point in the Caribbean is the promotion of an equitable and affordable healthcare system to stem the ravages of common diseases with significant morbidity and mortality. Promotion of health equity can be achieved by exemplifying the principle of distributive justice, which states, "studies should be designed to obtain knowledge that benefits the class of persons of which the subjects are representative" (4). In fact, research that has great potential to improve health in the Caribbean will not achieve this goal if distributive justice is not applied. As stated by Peter Piot, "the real double-standard lies not in the way the trials have been conducted but in the inequity in access to medicines in different countries" (5). This has practical relevance to the Caribbean region. The full effect of research is in the use of the knowledge acquired from the data but equally as important to intervene in the healthcare of relevant societies.

The second topic that I would like to address is the issue of the kind of research that we should be doing. The short answer is good research. But what is good research? Good research has several facets. As Altman states, "we need less research, better research and research done for the right reasons" (6). What Altman argues is that if a doctor uses the wrong treatment, either willfully or through ignorance, or uses the right treatment wrongly (such as giving the wrong dose of a drug), most people would agree that such behaviour is unprofessional, arguably unethical and certainly unacceptable. He suggests that we should be appalled when researchers use the wrong technique (either willfully or in ignorance), use the right techniques wrongly, misinterpret their results, report the results selectively, cite literature selectively and draw on unjustified conclusions. Yet these errors are common. We can all agree that general failure to appreciate the basic principles underlying scientific research coupled with the "publish or perish" climate leads to poor research. However, what is good research? Is it basic research or clinical research?

The distinction between basic and clinical research is not as clear-cut as we sometimes think. In fact, the dichotomy of basic and clinical research is rather vague and obtuse and similarly fuzzy as "prospective" and "retrospective" studies. In fact, a perusal of the journal *Clinical Investigation* will make the point forcefully if one tries to separate articles into basic and clinical categories. The dichotomy also implies methodological rigour and importance, the implication being that basic research is conducted with methodological rigour and is important. However, we all know that there can be sloppy research done at the cellular level as well as rigorous population based research. It is apparent to me therefore that thinking in terms of basic and clinical research is confusing and in fact, implies that we have lost sight of the most important reason for research, that of improving healthcare. Neither guarantees quality, neither is necessary for improving health, neither is sufficient for improving health. In fact, there are numerous examples in which we have not understood the fundamental basic mechanisms of disease processes yet have been able to improve health.

From my vantage point in paediatric intensive care, Reyes syndrome comes to mind in that with a dramatic reduction in aspirin use for fever, the syndrome has disappeared completely (7-8). Meanwhile, the basic scientist has lagged behind and to some extent is still trying to unravel the interaction between aspirin and the mitochondria. Other examples are the dramatic decreases in pulmonary infectious diseases worldwide with the improvement in nutrition and sanitation such that water and food borne diseases have decreased even before the organisms have been identified. In addition, more close to the Caribbean, sickle cell is a good example where we have known the molecular defect involved for over a quarter century, but any reduction in morbidity and mortality achieved has been the result of screening programmes and the use of prophylactic penicillin (9) and pneumococcal vaccine (10) and *Haemophilus influenzae* vaccines (11-12) to prevent overwhelming sepsis. There is no doubt that laboratory based research such as the development of surfactant vaccines and antiviral drugs has contributed greatly to health. What is important to recognize is that we need all research from bench to large scale epidemiological studies. The point is that research is multifaceted with a single goal: improvement of healthcare.

If the division of basic versus clinical is not helpful, then how do we clarify research? Kramer suggests two helpful dichotomies (Table), whether or not research is potentially useful (its potential to improve health) or whether or not it is methodologically rigorous (3). This dichotomy is

useful because it is a powerful reminder of what our ultimate research aims should be. Inevitably in the Caribbean, I would contend that one's research should address health issues facing a large segment of the population and associated with substantial morbidity or mortality. The second dichotomy is whether or not the research is methodologically rigorous. This indeed is a topic for another day, however, much has been written of research methodologies and their appropriate approach to particular questions. Suffice it to say that research is a team effort. We need consultants with expertise in research methodologies and biostatistical techniques to provide the expertise the clinician may lack. The situation is not dissimilar to the approach to a patient with complex pathology in clinical medicine

Based on the two dichotomies (Table) one can come up with a meaningful classification. Research in cell '*A'* is both useful and rigorous and therefore should be designed, funded, published and acted upon. In cell '*B'*, the research is rigorous but not very useful. Many of you can find examples of studies in this category such as the study of cystic fibrosis in the Caribbean population or whether the lack of potable water leads to diseases. Such rigorous research in the pursuit of trivial questions is a waste. It is a waste of talent and resources; however, the researchers may be convinced to pursue more fruitful endeavours. Cell '*C'* represents non-rigorous methods applied to potentially useful research questions. An example in the Caribbean would be a study on methods to control blood sugar in diabetics without looking at socio-economic factors such as diet, lack of exercise and regional myths. While the question of control is very important, the methods do not enable the researchers to address the question fully. It is possible that these researchers with assistance in developing a sound protocol may be able to answer these questions more fully and hence should be encouraged. Cell '*D*' on the other hand, represents the worst of both worlds: non-rigorous methods applied to non-useful questions. This type of research is a total waste of time, effort and money, and should be discouraged.

Before discussing the barriers to research, I would like to spend a few minutes to explore the ethics of research, especially as it applies to developing countries. An ethics-based approach to clinical research has to incorporate epidemiological methods that respect the particular needs and characteristics of the population that is involved in the study (13-14). In brief, investigators would need to address the impact of the research on the individual, the difficulty in establishing an acceptable balance of risks and benefits given higher morbidity in impoverished populations and the obstacles encountered in obtaining a valid informed consent (15-16). We need to define the acceptable balance of risk and benefits in that the degree to which an individual stands to benefit from a particular experimental intervention depends on the risk of death and disability resulting from the illness to which the intervention is targeted. This is indeed a tricky

Table: A Classification of Medical Research*
Adapted from Kramer MS (3)

	Useful	**Not Useful**
Rigorous	A	b
Not Rigorous	C	d

one. Guidelines need to be developed. It is tricky because given the higher incidence of adverse outcomes of infectious disease and nutritional deficiencies in impoverished regions, some interventions may have relatively greater benefits for the participants in these settings (*ie* zinc supplementation to reduce the incidence of pneumonia) (17). Therefore, a higher level of risk may be deemed acceptable if the overall risk-benefit ratio remains unchanged or improved. It is important that the investigators do all that is possible to identify, minimize and articulate any actual or potential significant risk to the research subjects. Articulation of risk must not be influenced by potential benefits to the investigators, their institutions or study sponsors.

I would like to address some of the barriers to research. It is often argued that clinicians should be more actively involved in research and that lack of involvement is due to shortage of time and funds. This may be partly true. More importantly, however, but a less obvious constraint is the differences of the philosophical foundations of clinical practice and research. Researchers must strive to abolish uncertainty, be unwaveringly committed to truth and rid of all bias. Clinicians in contrast must frequently manage patients in the absence of certainty, handle truth creatively and as part of professional obligations be willing to be biased on the patient's behalf (18). Other perceived barriers to research may be the issue of being too busy and overburdened by the demands of patients with no time left for research. This may be true for some, however, many have a fair degree of freedom to organize the working day.

The issue of funding has also been a constant source of frustration. While there is no doubt that some worthy projects are rejected, the number rejected may not be as large as billed. There are many creative ways of obtaining funds, especially in the Caribbean. With the financial assistance of regional governments who are interested in the well being of their citizens, as we heard from the Prime Minister of the Bahamas, there should be government sources of funding for research. We would be successful in convincing others to fund our research only if we have a clear vision of the issues we need to address and articulate these with conviction to others. Other barriers to research have been the lack of training in research and again needs to be addressed within the context of the Caribbean. An infrastructure for training young researchers, to support them in their research endeavours, as has been espoused for the academic paediatrician is relevant to other disciplines and should be considered (19). Other bodies have tackled similar

constraints and provided models that may be food for thought when designing a system for the Caribbean (20-22).

Another hindrance to research is lack of motivation or being "curiosity-challenged." This may simply be those who are blissfully unaware or unintrigued by research questions, but also those who are hampered by a lack of discipline or lack of ideas and flit like butterflies from one intriguing notion to the next, never settling down to the tedious but crucial task of organizing the logistics of finding answers. Another issue that may hamper research is the experts. While mentors need to be experts, they should be flexible and foster enthusiasm and sometimes offer support and encouragement to tackle important questions that may not totally interest them. Experts can be a double edged sword, as evidenced by the predictions of experts such "X-rays are a hoax" (Lord Calvin, physicist, circa 1900), "the cloning of mammals is biologically impossible" (J McCracken, Science 1984), and "there is no reason for any individual to have a computer in the home" (Ken Olsen, President of Digital Entertainment Corp, 1997).

Other barriers to research may be the drudgery associated with research when compared to clinical medicine. Clinical care is usually associated with rewards at many levels from patients, families and co-workers while research may be drudgery and is associated with rejection at many levels. That rejection is a fact in the life of researchers is highlighted by the facetious review of Columbus' proposal for his journey. It has been stated that his proposal would be rejected based on the following: "The entire basis of the proposal rests on the thesis, as yet unproven, that the world is round. Disapproval is recommended based on the lack of scientific merit. The aims… are certainly laudable but the rather naïve approach reflects a serious lack of academic research experience and training."

Finally, I would like to end on some of my research endeavours addressing the role of nitric oxide in lung disease that may be relevant to the Caribbean. As many would know, nitric oxide is a gas that serves numerous biological functions and in fact was designated the Molecule of the Year by *Science* in 1992. It is produced from L-arginine that is converted to citruline and nitric oxide, a reaction catalyzed by three nitric oxide synthase enzymes: NOS I (neuronal), NOS II (inducible) and NOS III (epithelial). Nitric oxide in the lung acts as a vasodilator, neurotransmitter and a bronchodilator. However, nitric oxide when induced by asthmatic inflammation produces large amounts of mucus, induces capillary leakage and inflammation leading to the characteristic symptoms of asthma. As a result of its recognition, as a marker of inflammation and the fact that it can be measured in exhaled air, we embarked on a series of experiments to further refine the methodology in measuring nitric oxide in exhaled air. Based on our studies (23-25) and that of others, the American Thoracic Society, American Lung Association and the European Respiratory Society developed guidelines for measuring nitric oxide in children and adults (26-27).

Based on the ability now to measure inflammation in asthma, we have conducted a series of experiments which in the interest of time I will keep very brief. We have found that exhaled nitric oxide reflects asthma severity and asthma control and may be used to monitor disease activity, the need for steroid therapy and compliance to steroids (28). More recently, we have also found that monteleukast has anti-inflammatory properties as judged by exhaled nitric oxide in asthma in patients with a specific LTC_4 synthase $A_{-444}C$ polymorphism (29).

Equally relevant to the Caribbean are investigations looking at the level of exhaled nitric oxide in acute chest syndrome of sickle cell disease. Acute chest syndrome is a common cause of incapacitating pulmonary sequelae and may result in 25% of premature deaths in patients with sickle cell disease. Nitric oxide derangements are implicated in acute chest syndrome in that these patients during their acute phase may be hypermetabolic and have decreased serum arginine and increased nitric oxide metabolites. Indeed, inhaled nitric oxide has been therapeutic in acute chest syndrome (30). Moreover, as many of you would recognize, there are individuals with sickle cell disease who have recurrent acute chest syndrome while others do not. This suggested to us that there might be a genetic explanation likely: nitric oxide synthase polymorphisms. We therefore conducted a series of experiments and found that those with a specific polymorphism of the NOS I gene were more prone to acute chest syndrome (31). We concluded that exhaled nitric oxide is a sensitive marker of individuals prone to acute chest syndrome. Genetic analysis and prospective identification may be possible and lead to therapeutic interventions for this disease. We therefore feel that this research would be of benefit to those affected with this disease in the Caribbean.

Finally friends, it has indeed been a pleasure to share some of my thoughts on research. I am very grateful for the opportunity and look forward to research endeavours in the Caribbean. Judging from my own career, there will be tough times, but I would like to close with a quotation of James Watson, who stated, "Moving forward may not be for the faint of heart. But if the next century witnesses failure, let it be because our science is not yet up to the job, not because we do not have the courage to make less random the sometimes most unfair courses of human evolution." Watson was referring to the genome project; however, his sentiment is applicable to all research. My final thoughts are that we should have the courage to pursue answers to questions that would be beneficial to the Caribbean region and to relieve the burden of illnesses that befalls our people. Once again, thank you very much for this opportunity.

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