CAPACITY-BUILDING IN BIO-MEDICAL RESEARCH IN PAKISTAN

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ABSTRACT

The edifice of any research, may it be scientific or social, stands on 3 basic pillars:

1. *Appropriate manpower (trained experts, competent personnel);*
2. *Adequate Infrastructure (space, physical environment, equipment, library, etc);*
3. *Incentives (well defined goals, reward and punishment.*

Based on this principle, it is no wonder that very little research is carried out in this country. There are no more than 3,000 science PhDs in the country, with an addition of hardly 30-50 per year. Only 90 persons are engaged in R&D per million of population, as compared to 4100 in Japan. Less than 0.4% of our GDP is spent on R&D, whereas a minimum of 1-2% is essential. Thus, Pakistan contributes less than 0.04% towards the world's research publications, out of which there is a negligible amount in the field of health-sciences.

On the other hand, even a cursory look at the health-indicators presents a highly discouraging picture. Infant mortality of around 86 per 1,000 live births is the highest in Southeast Asia; even Nepal has 73/ 1,000; so is childhood-mortality (at 110/1000). More than 50% of pregnant women suffer from anemia. Tuberculosis still accounts for 18% of mortality in the communicable disease category, while hepatitis and AIDS are increasing alarmingly.

Pakistani scientists, especially biomedical scientists cannot remain indifferent to this situation. However, the basic problem with biomedical research is that there are only a few trained scientists in this field. Medical professionals, by definition, have no formal training in research. There has also been a lack of collaboration between clinicians and basic scientists to carry out biomedical research. There is, thus, an urgent need for such scientists to work together, as is universal in technologically advanced countries. Basic scientists in the fields of biology, biochemistry, biotechnology, biophysics and bioinformatics, etc, need to work together with clinicians in trying to understand health and diseased conditions of the human body. A concerted research effort is required to arrive at an accurate diagnosis of the disease and to adopt an appropriate therapeutic regime. Such research has become all the more relevant in this post-genomics era, as well as, with the advances made in stem-cell research arena. These recent developments in biomedical technologies have the potential to change the face of control and management of disease. It is imperative that Pakistani basic-scientists and clinicians are provided an institutional platform, where they can work together, to evolve a state health-care arid management plan. COMSATS Biomedical Research Center is being established as a step in this direction. Details of the capacity-building and research plans of the Center will now be discussed...

INTRODUCTION

At the beginning of this century, with the completion of human genome project, many mysteries and puzzles were being unfolded and many more are waiting to be explored in the field of human health care. The last century has witnessed the zenith of Physics and nuclear technology but this century undoubtedly can be called the century of Biotechnology and its derivative sciences, such as Biomedical sciences.

Like the rest of the third-world countries, Pakistan also suffers from a primitive and quite dysfunctional, health-care system. What can be said about the general health-conditions of a population, 60% of which does not have access even to clean drinking water. Even a cursory look at the health statistics in Pakistan reveals a depressing scenario.

According to the latest statistics available (for the year 2001-2002), Infant mortality in Pakistan is 83.3 per 1000, which is the HIGHEST among many South Asian and far eastern countries; it is even higher than Nepal (with 73.6 per 1000) and compares pathetically with a country such as Malaysia (with only 7.9 per 1000). Even childhood mortality (under the age of 5

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years) per 1000 persons is the highest in Pakistan at 110.3, as compared to that of Nepal (104.7) and India (87.7).

Almost 35% of children remain undernourished, while 50% of pregnant women in our country suffer from anemia. This is inspite of a major effort of children-immunization program, being carried out during the last several years in the country. Many dreaded communicable diseases, such as Malaria, Acute Diarrhea, Dysentery (Both amoebic and bacillary) and Tuberculosis, are quite rampant and the current scenario shows that their percentage is very high among the world population. Acute Diarrhea has been the biggest killer and contributes almost a quarter of the total mortality. Even respiratory tuberculosis, which has been eliminated from many parts of the world, causes almost 18% of the mortality among the communicable diseases category. In 1998-99, there were as many as 105,000 cases of Malaria reported, indoors in various hospitals of Pakistan: a disease which has been eliminated from many parts of the world. More recently, cases of Hepatitis and AIDS are also increasing at an alarming rate; more than 13,000 cases of Hepatitis were reported indoors in Pakistan during 1998-99, while it has been estimated that there may be as many as 70,000 to 80,000 HIV positive cases in this country by now. These figures become more frustrating when one considers the fact that all these communicable disease are "avoidable" through better education, personal and environmental hygiene and through research.

Pakistan has been struggling due to some basic problems to provide basic medical care and health-facilities to its citizens during the last 50 or so years of its existence. Very briefly, these problems are:

i Over population
ii Lack of Education
iii Lack of Resources, both human and financial
iv Poor Research and Planning

These are discussed below:-

i Overpopulation

Pakistan's population has increased from 30 million in 1947 to about 146 million. The population growth-rate of 2.4% (for the year 2000) and projection of 2.1% for the year 2002, is the second highest among several of its neighboring countries (only Bhutan, with 2.9% has higher). This is an alarming situation, which needs to be tackled urgently. The family planning program has been able to cover only about 50% of the population and is expected to cover 70% of population by the end of 2003. Unfortunately, however, this program has not been able to achieve its goals so far, due to a large number of reasons, including our social and religious norms. It can be easily speculated that if such a trend in population-growth continues, then many of the public-health and welfare programs will continue to remain inadequate, despite substantial inputs, both monetary and human.

ii Lack of Education

It has been well established that education is the key to socio-economic growth and development of a country. It not only enlightens but also prepares people to take part in the opportunities available in the labor market, thus enabling them to escape poverty.

There has been a gradual increase in our literacy-rate over the past decade and it has now reached almost 45-50%. There has also been an increase in the number of Primary, Middle, Secondary, Higher Secondary institutions, Colleges and even Universities in the country but their number is still far less than what is required for universal education. In many of our rural areas, the literacy rate is still below the 30% mark. The overall rate of less than 50% is still among the lowest in the region and needs to be improved dramatically if we are to compete with the rest of the world and, more specifically, in the context of the present discussion, we need to educate our masses about the potentially deadly diseases and the importance of their timely reporting. With the beginning of the post genomic era, it is also important to orientate our public and policy-makers in the right direction so as to set the stage for getting the maximum use of available genome data, to resolve our indigenous as well as global health problems.

iii Lack of Resources

There is a pathetically low financial investment in the health-sector in this country. Pakistan spends about 0.7% of its GNP on health in public sector, as compared to 6-15% which the industrialized countries

spend, or even 2-5% of GNP spent by many developing countries. No wonder we have a ratio of one doctor for more than 500 persons and one nurse for more than 3600 population, while there is only one dentist for more than 31,000 people. There is only one hospital bed for more than 1400 persons! It is quite obvious that in order to improve these conditions, infrastructural facilities need to be increased substantially, both physical and human.

iv Poor Research & Planning

For a sound health-delivery system in a society, a well established Health Research System is essential. Without sounding dramatic about it, it can be stated fairly accurately that health research has never been more than rudimentary in this country. Not only are there very few researchers in this field, but there is almost a complete lack of organizational and financial support for the researchers in the areas of health and nutrition. Pakistan Medical Research Council (PMRC) is the only organization that has been trying to set up a viable Health Research System in Pakistan, with relatively very little resources at its disposal. In fact, very little research has been conducted so far in the country in the field of medical sciences. What can be expected in a country where there are no more than 3000 Ph.Ds in all Science disciplines, with an input of 30-50 PhD's a year! Then, not all of these "experts" are engaged in research. According to a recent estimate, there are only 90 persons engaged in R&D in Pakistan per one million population (compared with 4100 such persons in Japan!). To make matters worse, Pakistan spends less than 0.4% of its GDP on R&D (as compared to at least 1-2% recommended for a meaningful R&D). No wonder, Pakistani scientists contribute less than 0.04% to research publications of the world (as compared to more than 2% by India). It is quite apparent that a major endeavor is needed in this area if Pakistan is to set up a decent Health Research and Delivery System for its people.

REVIEW OF CURRENT HEALTH-RESEARCH IN PAKISTAN

As stated previously, very little biomedical and clinical research is being carried out in Pakistan. Recently, PMRC has prepared a guideline for action i.e. an operational plan for the period 2001-2006, for the development and strengthening of Health Research System in Pakistan. How successfully PMRC will be able to achieve the objectives of this plan will have to be seen after the completion of the program. In the meantime, PMRC has been able to set up 18 Research Centers so far in 90% of the public-sector undergraduate and all postgraduate medical institutions of the country. However, the present arrangement has not worked satisfactorily till now.

Apparently, trained manpower, financial resources as well as logistics are all lacking, presently, to achieve the desired results. Thus, PMRC is revamping the whole strategy. An in-depth analysis of i) priority areas of medical research ii) identification of capable institutions iii) technical, financial and material sources availability, and iv) incorporation of the results of the research into policy-making, is planned to be carried out in the next few years. That too, with expected national and international fiscal assistance. The following main parameters to be studied during the proposed 5 years (2001-2006).

- Magnitude of the disease/condition burden
- Current interventions, in place of those conditions
- Potential impact of research on policies and interventions

PMRC is also planning to bring about its restructuring, in order to achieve its goals in a more effective manner, including a significant decrease in the number of its Research Centers; from 18 to 5 in total, but located at major institutions with well established communication-mechanisms.

WHY LACK OF MEDICAL RESEARCH IN PAKISTAN

There are a number of reasons for an almost complete absence of research in the medical field in this country. Interestingly enough, the research which is carried out is that of a survey type or statistical in nature. For example, the Annual Report of Director-General (Health) for 1998-99 lists 6 publications by Health Services Academy (HSA), Islamabad. The titles of these publications are:

- "Occupational safety and Health in Pakistan"
- "Perceptions of obesity and diabetes in societies in transition"
- "Environmental considerations in nutrition"

- "Role of economic and social development on nutritional status of women with reference to South Asia: An agenda for public policy"
- "Privatization of public hospitals in Pakistan; issues of quality, cost and quality"

It is quite apparent that there was no experimental or clinical research carried out and published during the year under review.

As pointed out earlier, there are a number of reasons for this state of affairs, in terms of basic medical research, in Pakistan.

Firstly, as pointed out earlier, there is a lack of research persons in all sectors of science. There has been a little effort to develop what is referred to as "Science Culture" in our society. Scientific research has had little incentive or reward till very recently. Only this year, a few scientists in the country have been given financial rewards, based on the "Impact Factor" and "Citation" record of their publications. (It is, however, entirely a different matter that these publications were mostly based on research work carried out in foreign countries!!!). It is quite disheartening to note that there were a total of only 669 publications in the year 2000 emanating from Pakistan, which was about 0.04% of the total publications. This number was even less than Nigeria (933) or Morocco (1110)! Such was the output from various disciplines of science, such as Chemistry, Physics, Agriculture and Biology, etc., in which there are well trained scientists (with Ph.D degree) in the country. What can be expected from medical (clinical) graduates, who, by and large, have no formal training in conducting research. Only recently, a few of the medical graduates have enrolled into M.Phil or Ph.D programs within or outside the country. Such research-trained clinical scientists have not yet made a tangible mark on the overall medical research arena in Pakistan.

The second most important reason for lack of interest in research is financial. Due to an acute shortage of physicians in the country, most of them are extremely busy in direct patient care, both at hospitals, as well as in their private practice. It follows that this becomes financially very rewarding. These clinicians would, naturally, spend time in this lucrative activity, rather than spend time in research, which is highly time-consuming and does not carry even a fraction of the rewards.

Thirdly, there is an almost total lack of interaction between basic scientists and clinicians in our country. It is a norm in the scientifically advanced countries that clinicians interact very closely with basic scientists in carrying out their research. It is quite obvious that the generation of new knowledge in any aspect of human existence follows extensive experimentation on the closely related species of experimental animals, such as mice, rats, guinea pigs, cats, dogs and monkeys. The genetic make up of such animals is very closely related to humans and so are, therefore, all life processes going on in them. The bio-scientists, may these be anatomists, physiologists, biochemists, cell biologists, geneticists or developmental biologists, are all involved in the study of the human body, through the use of other life-forms, including micro-organisms. A lot of information (data) is thus generated by basic scientists, in terms of all life-processes, as these occur in animals, which is then taken up, studied, analyzed, and used by clinicians in the understanding of what goes on in humans. In fact, a survey carried out by American Medical Association in 1989 found that 99%, of more than 500,000 physicians believed that animal- research had been essential for medical progress. These were the studies on mice, which led to the progress in gene-therapy as a cure for Cystic Fibrosis in children and young adults. Similarly, dogs were used to develop angioplasty techniques, and a lot of research on Alzheimer's disease was carried out on monkeys. Animal studies are required by law to be carried out on all medical drugs and procedures, before these can be allowed to be tested on human subjects.

Unfortunately, this relatively simple concept has not yet been comprehended by our scientists. Till today, our medical colleges tend to compartmentalize basic and clinical sciences and treat them as separate entities, instead of two parts of a whole. This has resulted in these scientists working in isolation, with very little extrapolation and application of basic biological research onto human health and welfare. No wonder, clinical scientists have not been able to carry out any meaningful research in various fields of health. It is therefore, about time that our basic scientists and clinical scientists get together (as is

done in the developed world) to carry out research for the betterment of human health. The major draw-back in this regard is that our policy-makers were not focused to plan the health-policy to address the real as well as potential health threats. Temporary and short-term measures have been adopted in the past to tackle health-problems and real research, according to the ever changing needs of the country, is non-existent. This aspect of medical or clinical research has attained significant importance, in the light of many recent scientific advances in both preventive and therapeutic practices.

One particular scientific achievement, which has potential to give new out look to the whole health-care system in the coming years, pertains to "functional genomics" i.e. the science dealing with the functional characterization of genes belonging to complex human genome and disease-causing pathogens.

It was visualized well before the completion of human genome project (2001) that the explosion of information will bring a revolution in medical research and patient-care. With the completion of genome sequencing of the deadly human pathogens, and with the human genome being sequenced already, it would be possible to understand how genes associated with particular functions are controlled, regulated and interact with each other, in particular environment, to control the complex biochemical functions of the living organisms during the disease process.

Thus, this research will have major benefits for the prevention, diagnosis and management of many diseases, including both communicable and non-communicable diseases. Research in genomics will help us to understand the host-pathogen interaction and the strategies deployed by the pathogen to avoid the host-defense mechanisms. This information, in turn, will help us in better diagnosis and development of new vaccines and drugs.

BIO-INFORMATICS

Bioinformatics is one of the most exciting areas in biomedical sciences during the transition to the 21st century. By definition, science of Bioinformatics has to be multidisciplinary in nature, involving biology, medicine, mathematics and computer sciences. In simplest terms, Bio-informatics concerns the creation, maintenance and analyzing of databases of biological information.

The objectives of this newly emerging science are to enable researchers to access efficient tools for managing and interpreting the ever-increasing quantities of genome data and for making it available to the research-community in an accessible and usable form. Its main focus is on Molecular Biology i.e. computational modeling of regulatory and metabolic pathways, protein structure and design and characterization of the genomes of organisms, including human genome. The focus of the project is to move from the "wet lab" with its gels, sequences and PCR machines to the "dry lab" of hardware, software and algorithms. A researcher equipped with an internet-connected computer, a working knowledge of the sequence-analysis techniques can provide a surprising insight into the macromolecular architecture of a completed genome.

Genome sequences are of little value without the powerful tools of bioinformatics and functional genomics. The vast amount of the new data will provide us not only with information on bacterial diversity and evolution, but also with the ability to probe the inner depths of some of mankind's oldest enemies (and some of the newer ones).

Pakistan, already trying to catch up with other countries in acquiring new technologies, such as Biotechnology and Information technology, cannot afford to lag behind in this endeavor. The research will focus on developing bioinformatic tools and resources for data-storage, mining and processing; developing special computational biology approaches for *in silico* prediction of gene-function and for the simulation of complex regulatory networks. Considering all these facts, and to materialize them, we need to set up an infrastructure for genomic research supported by a well-established bioinformatic laboratory.

DIAGNOSTICS

The complete sequencing of the human genome, announced in 2001, marked the culmination of unprecedented advances in the science of genomics, the study of genome and its functions. The availability of genome-sequences for many living organisms

clearly has important implications for improvement of health, and it has been widely predicted that elucidation of the sequences will lead to a revolution in medical research and patient care.

Any benefits that result from the latest advances in genomics research, in clinical applications in many diseases, will be irrelevant to countries that do not have functioning health-care systems. However, conventional, tried and effective approaches to medical research and practice must not be neglected while the medical potential of genomics is being explored. DNA diagnostics prove to be a valuable tool to identify the pathological agents which are otherwise difficult to identify by conventional methods, such as culture, and also for assessing the level of activity of chronic viral infections, such as Hepatitis C infections. This will give us accurate information for future drug design or vaccine-formulation according to our indigenous needs, keeping in mind the target gene-sequence of the pathogenic organism.

Molecular biology techniques, such as Polymerase Chain Reaction (PCR) and Enzyme-linked immunosorbant assays (ELISA), have proved to be rapid, cost-effective and highly sensitive tools in modern diagnostics. For instance, beta thalasaemia is an autosomal recessive genetic abnormality resulting from the reduced/absent synthesis of beta-chains of the globin part of the haemoglobin molecule, which in most cases is due to point mutations in globin gene on chromosome 11. Pre-natal genetic counseling/diagnosis will prevent this social, emotional and economic trauma, which is also prevalent in Pakistan. Similarly the strong molecular biology technique of multiplex PCR has been successfully used to diagnose various diseases like Cholera. The unexpected and explosive entry of the O139 serogroup of Cholera has complicated the diagnosis of the disease, whereas current rapid tests are all focused on the O1 serogroup. Multiplex PCR method is capable of providing multiple information directly from stool-specimens in approximately 5 hours. The potential for using genes themselves to treat disease, known as gene-therapy, is the most exciting application of DNA science. “DNA chips” is another fascinating idea in modern science, which can be used to screen enormous number of potential target DNA-sequences and is therefore ideal for examining clinical samples for microbial pathogens. However, the time-scale for this diagnostic tool to be operational is difficult to predict. These routine diagnostics can also act as a bridge in linking the clinicians and basic scientists and also give financial boost to the biomedical faculty in conducting meaningful research in parallel.

CONCLUSIONS

This brings us to the final point of the present discussion, which is how we can proceed to carry out research in this direction. Although it is obviously a difficult proposition, especially in the context of our political, economic and social milieu but, sooner or later, we have to realize the importance of “genomics” in transforming the status of health-care in our country. Therefore, this is the time to get ourselves organized and plan for the genomics era, in order to ensure that the advances of the genomics revolution are effectively and efficiently applied to improve the health of our population. We should also be conscious of the reality that much of the genomics research and development is performed, and owned, by private-sector interests in the developed world and hence is market-driven and therefore, instead of looking to some other developed nations to come and rescue us from our indigenous health-related issues, we better move in the direction of self-sufficiency in Biomedical sciences with the changing interests of big pharmaceutical industries in the post-genomic era. This can be done either by strengthening the existing or establishing new centers and institutions engaged in genomics research, with a view to strengthen national capacity and accelerating applications of the advances in genomics relevant to the country’s health-problems.

Lastly, one needs to re-emphasize the three well known basic ingredients for carrying out any meaningful research. These factors are:

- Trained manpower
- Adequate infrastructure
- Appropriate incentives

Unfortunately, even these basic factors are lacking in our country. However, let this meeting / workshop be the first step in the planning and action in the direction of sufficiency in this regard. The first and foremost thing with reference to building our capacity in Biomedical research is to train scientists/researchers so that they can acquire the necessary expertise in

various aspects of biomedical research, such as functional genomics and bioinformatics as explained already. This would obviously involve clinical scientists, basic scientists, paramedical experts and technicians. The need for all health-professionals to have competency in various fields of biology and medicine is therefore essential. A vast majority of existing clinicians, who have practically no training in carrying out scientific research, need to be given short and long-term training courses to familiarize them with modern research-techniques and their applications.

Similarly, many of the basic scientists in the fields of biology, chemistry, physics, mathematics and engineering will need to be trained in health-related problems. Auxiliary paramedical/technical staff needs to be educated and trained to carry out routine clinical practices and so on. This can only be achieved if necessary infrastructure is in place, in the form of laboratory facilities and equipment---a giant effort in itself. Thirdly, realistic incentives, both professional and economic, need to be provided to all these personnel, if we are serious in our efforts to provide better health care to our people.

COMSATS Institute of Information Technology does plan to embark upon this effort, by setting up their Center for Biomedical Research (CBR). It is hoped that this initial endeavor would lead to the setting up of many more biomedical research centers in the country, so that better health-care system can evolve in Pakistan.

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