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Is Medical Research at the Right Track

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Abstract- *Background:* As it is well known that a disease is any disorder or incorrectly functioning organ, part, structure or system of the body resulting from the effect of genetic or developmental errors, infection (caused by pathogenic microorganisms), poisons, nutritional imbalance or deficiency, toxicity or unfavorable environmental factors [1,2]. Fortunately, during twentieth century, medical investigation and research have been diagnosed, treated, cured and prevented many diseases. The primary treatment is through using vaccines and drugs, which are required and beneficial. Medical research is a vital to the health and wealth of societies, as scientific knowledge can improve health and the quality of life.

The objectives of this article are to discuss many topics (immunity, immunogenetics, molecular genetics, pharmaceutical, histopathology and other relevant subjects), to get what has medical research done to improve health of human, to figure out whether these research are at the right track? and to suggest recommendations for future medical research.

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Life Span: It is written that life span of ancient people were more than hundred years. A progressive decline over the generations from Adam's 930-year life, to Noah's 500 years, to Abraham's 175 [3]. As the life was so simple and there was no pollution, no food preservative, no drugs abuse, no depression, no hypertension, no pesticides, no insecticides, no competence, no hypocrisy and no hate. Mean life span varies with susceptibility to diseases and other environmental (risk) factors [4, 5].

Immunity: Immunity refers to having a resistance to a disease or illness. It is well documented that natural immunity possessed by individuals at birth prior to exposure to pathogens or antigen and that includes components such as neutrophils and natural killer cells, which provide an initial response against infection [6]. Maternal passive immunity (Innate immunity) is a type of naturally acquired nonspecific passive immunity, and refers to antibody conveyed to a fetus or infant by its mother. It provides resistances through several physical, chemical and cellular approaches. Passive immunity is also provided through the transfer of IgA antibodies found in breast milk that are transferred to the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies. Subsequent general defenses include secreted chemical signals (cytokines), antimicrobial substances and phagocytic activity associated with the inflammatory responses. Through these approaches, innate immunity can prevent the colonization and spread of microbes. On the other hand, naturally acquired immunity occurs through contact with a disease causing agent. Whereas, artificially acquired immunity develops through vaccination [7, 8 & 9].

Immunogenetics investigations showed the normal immunological pathways and the identification of genetic variations that result in immune defects, which may result in the identification of new therapeutic targets for immune diseases. Studies have indicated that host genetic factors are major determinants of susceptibility to infectious diseases [10, 11]. Also found high heritability estimates (proportion of genetic variation to the total phenotypic variation) for many immune responses to pathogen antigens [12, 13 &14]. Successful research results were obtained, in which candidate gene have implicated several immunogenetic polymorphisms in human infectious diseases. Human Leukocyte Antigen (HLA) variation has been associated with susceptibility or resistance to malaria, tuberculosis, leprosy, AIDS, and hepatitis virus persistence [15]. Variation in the tumor necrosis factor gene promoter has been reported to associate with several infectious diseases. It is likely that susceptibility to most microorganisms is determined by a large number of polymorphic genes, and identification of these should provide insights into protective and pathogenic mechanisms in infectious diseases. Genetic variations among individuals may affect susceptibility (or resistance) to various diseases [16]. It is important to identify genetic variations and its contributions to naturally acquired immune responses. This may lead to better health care of human being. Furthermore, most of the molecular genetic variations in immune responses remained unexplored. Therefore, the genetic variations among individuals within families in antibody response need to be investigated. As such investigation in human may be not easy it is recommended to investigate such issue in mice or Guinea pigs as a model for human. Results revealed that seven antibody isotypes of IgG4 heritability estimates were found to be high (above 0.5) of all isotypes responses to all antigens, indicating that IgG4 responses are most strongly genetically regulated [16]. Furthermore, they indicated that genetic variation in regulation of cytokines may also contribute. On the other hand, there is considerable heterogeneity in immunological parameters between individuals, but its sources are largely unknown. Non-heritable influences explain much of the variation in immune measurements [17].

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Vaccination: Vaccines are suspensions of infectious agents used to artificially induce immunity against specific diseases. A tremendous amount of biological events are triggered which are essential in developing immunity. Results revealed that cytokines are low-molecular weight proteins that control, coordinate, and regulate various immune or inflammatory responses. Recently, gene therapy and DNA vaccination has been used to produce memory against a number of cytokines that promote inflammation. Antibodies to the product of each inserted gene were produced. These antibodies were found to prevent the effects of the cytokines. Recent vaccine research and development has focused on recombinant DNA vaccines as a way of duplicating natural immunity, but the findings demonstrate that they work by suppressing the immune system as well. DNA vaccines consist of a bit of DNA containing a gene for a marker from the pathogen. The idea is that when the DNA is injected into the muscle tissue, it works its way into cells where it is incorporated into cellular DNA. Recent research indicated that instead of being immunized to the protein encoded by a DNA vaccine, it actually learns to tolerate it [18]. However, when later injected with the same protein, no antibodies were developed at all. This finding indicated that the possibility that a DNA vaccine could convert someone who normally would be able to clear a pathogen-albeit they might get sick first, to someone who would be unable to clear it at all. The science of immunology is on a fast track due to recent advances in molecular biology and genetics research. Though there is still much to be done. Thus it will need an increased emphasis on nutrition, exercise, and structural integrity of the human frame, all of which maximize the body's innate healing power. Lately, there have been complaints from individuals about vaccine side effects and the lack of long-term scientific studies and safety data on vaccines especially; nowadays there are more than 200 vaccines in use. Medical research in vaccination technique has successful stories and impact through eradication of many diseases in the past 100 years including polio, smallpox, whooping cough and diphtheria [19].

Diseases and Drugs: A disease is a particular abnormal condition, a disorder of a structure or function, which affects part or all of an organism. Disease is often associated with specific symptoms and signs. It may be caused by external factors such as pathogens, or it may be caused by internal dysfunctions particularly of the immune system such as an immunodeficiency, or hypersensitivity. There are four main types of disease: infectious diseases, deficiency diseases, genetic diseases and physiological diseases [2]. Medicines are commonly used worldwide. Drugs are used to diagnose, cure, treat, or prevent disease [20].

Drug therapy is an important part of the medical field and relies on the science of pharmacology for continual advancement and on pharmacy for appropriate management. Drug discovery and drug development are complex and expensive endeavors undertaken by pharmaceutical companies, academic scientists, and governments. Recently, there are many successful results, implications and advancement in pharmaceutical research and industry, especially when technology of sequencing of human genome where applied. Such technique allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease modifying in a process known as reverse pharmacology. Hits from these screens are then tested in cells and then in animals for efficacy. Moreover, scientists have been able to understand the shape of biological molecules at the atomic level, and to use that knowledge to design drug candidates. Modern drug discovery involved the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy (expensive, difficult and inefficient process) with low rate of new therapeutic discovery [21]. In 2010, the research and development cost of each new molecular entity (NME) was approximately US$1.8 billion [22]. As it included pre-clinical research (microorganisms/animals) and clinical trials (on human) and may include the step of obtaining regulatory approval to market the drug. Nevertheless, drugs can help and keep people safe, but some are dangerous if they are used in the wrong way [23]. The controversial role of pharmaceutical and how diseases can be prevented is a vital issue to be investigated in details. There are many issues to be investigating such as mixing drugs that interact adversely and a drug overdose or poisoning besides that some people are sensitive to various drugs and how they are able to metabolize them. It is important to investigate the effect of drugs used and its consequences. It was reported that drug abuse had side effect on the gastrointestinal tract (esophagus, small intestine, colon, stomach and duodenum and jejunum). Furthermore, it has been showed histopathology consequences of drugs induced lesions, ulcers, hemorrhage, necrosis and gastritis [24]. Moreover, many bioactive natural products have been identified and characterized from cyanobacteria. Some compounds are of medical and/or pharmaceutical importance as they exhibit antimicrobial, antifungal, and anticancer activities [25]. However, some of these metabolites are toxic toward a great variety of

organisms, including humans. Histopathologist researchers have been investigated the toxicity of such compounds via sectioning, staining and evaluation of cells and tissues. Furthermore, they focus on how a tissue is interacting with other tissues or drugs. Histopathological findings provided a correct diagnosis and assessment of many drug-induced allergies or diagnosis of new drugs toxicity or any adverse effects in patients. It highlights issues in evaluation of carcinogenicity of drugs [24]. Recently, it was reported that scientifically evaluation of biomarker performance in relation to histopathologic changes is essential as guidance for qualification process for drug development [26].

Human Genome Project: In the middle of the twentieth century, Watson and Crick revealed the chemical basis of heredity with their discovery of the double helical structure of DNA. Recently, sequence the entire human genome (Human Genome Project, HGP) has become an international effort, to develop a catalog of human DNA variations. While DNA sequences in peoples are 99.9% identical to each other, the 0.1% of variation is expected to contain many clues about the genetic risk for illnesses [27]. Technology developed to study the expression of many genes at once. The new technique can allow researchers to observe in a single experiment whether as many as 10,000 genes are turned on or off in various cells or under different conditions. Such studies will help reveal how different tissue types differ and what alterations in gene expression accompany the development of diseases. Such analyses have already helped find differences among tumors that otherwise seemed identical. Because large-scale experiments are flooding researchers with information, a field called computational biology is emerging and will become increasingly important for analyzing all these data [27].

Medical Research in the Twenty-First Century:

Having the human genome sequence and knowing the DNA spelling variations among people will help reveal which genes contribute to the risks for common diseases. This will be a challenging task. For diabetes, for example, researchers expect that five to ten - and perhaps more - genes are involved, all of which have forms that increase the risk for disease slightly. Those genes interact with each other and with the environment in complex ways. Finding a gene involved in such diseases is many times harder than in cases where a disease stems from variations in a single gene.

Even so, researchers are optimistic that by precisely diagnosing different forms of diseases like diabetes, heart disease, and cancer and by developing a large catalog of genetic variations, they will begin to find genes for some of the most common illnesses in the near future.

Researchers will need to develop and apply methods that analyze many drugs at a time for their potential affect on disease-related genes and gene products. The pharmaceutical industry has been gearing up for this opportunity, and most pharmaceutical companies now expect that the majority of future drug development will come from the field of genomics. New, efficient ways of analyzing the effects of many drugs should identify those that block or stimulate particular genetic pathways. Genomics is likely to help allow the prediction of individuals' responsiveness to particular drugs, since variations in drug response often stem from genetic differences. For example individuals break down particular drugs at different rates. Researchers are beginning to correlate variations in the spellings of genes with variations in responsiveness to different drugs. This new field is called pharmacogenomics and promises to make prescription of drugs a much more individualized affair in the future [27]. By 2020 the impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for predicting drug responsiveness will be standard practice for many drugs. New gene-based "designer drugs" will be coming on the market for diabetes, hypertension, mental illness, and a long list of other conditions. The diagnosis and treatment of cancer will likely be transformed. By 2020, it is likely that every tumor will undergo precise molecular fingerprinting, to catalog the genes that have gone awry, and therapy will be individually targeted to that fingerprint [28].

Concluding Remarks: Although, it was reported that progress being made in individual's longevity is entirely due to medical and public-health efforts, rising standards of living, exercise, better education and healthier nutrition are also vital issues to be considered. Among medical researchers, progress and success is assessed according to professional and objective criteria such as volume of publication output in scientific journals and associated citations, securing research grants and running a large-scale research by multidisciplinary team. Outside the system, people want to know the impact of medical research on health of human and mortality [29].

God created man in his best form, especially when he lives in his natural environment. That means that his body is designed to be able to defend itself against foreign invaders. Nevertheless, with currently existing high risk environmental conditions, mankind has to cope with such situation. Therefore, many questions should be investigated in details and addressed to medical researchers, among these are the followings:

- What are the contributions of genetic versus non-genetic (environmental) factors to disease incidence?
- Is there any specific age at which active gene become inactive (or vice versa)? Or is there any

specific age at which gene (allele) under specific environmental factors show its expression or switched off? Are oxygen (fresh air), chemicals, depression and hypertension play important role in incidence of diseases?

- How long can allele tolerate or how fast can allele respond to unfavorable environmental factors?
- Why do many people of more than 70-year old still healthy and enjoy life without serious diseases? Is there any variation in gene stability or sensitivity, and at what age?

Final Conclusion and Suggestions: It is concluded from this review that although huge scientific information and results of much medical research is just few drops from ocean. Moreover, although there were too many successful stories, achievements and progress made in medical scientific research, nobody knows where and how far medical research is going. Even though, people should be optimistic.

It is suggested that integrated multidisciplinary international team (pharmacists, molecular biologist, pathologists, geneticists, toxicologists and statisticians) should work together in all medical research activities to have more efficient and tangible impact on health of human.

Accordingly, below some suggestions to medical researchers:

1- A well defined experimental design should be followed by medical researchers to investigate sequencing the entire human genome to develop a catalog of human DNA variations, The experimental design should contain many experimental groups to identify risk for diseases incidence via screening people who are healthy and highly resistant to diseases, versus people who developed the disease across various age groups. Age groups may be: more than 80, 70 - 80, 60 – 70, 50 - 60, 40 – 50 and less than 40 years old. Moreover, each age group can be breakdown to whether person is smoker or nonsmoker and whether he is living in polluted or rural area. Such experimental design allow to investigate and identify the highest gene frequency (represent best disease resistant gene) in smoker, living in polluted area of healthy advanced aged person, which may suggest the possibility of that gene(s) to be responsible for diseases resistance and/or influence life span of peoples.

2- It needs well defined research and investigation for increase the level of natural immune (antibodies) to achieve natural disease resistance. As the human body is designed to be able to defend itself against foreign invaders. Therefore, a chance to natural immunity to defend body should be considered (given) in many diseases.

3- Nutrition plays an essential role in human health. Poor diet quality influences weight status and cardio-vascular health. Thus medical research should examine nutrition (nutrients balance and interaction among essential amino acids, essential fatty acids, minerals and vitamins) at all stage of life and investigate related issues including immunity and disease resistance. This will contribute to the understanding the role of diet in many diseases and also to undertake whether improve diet can improve resistance to disease risk. In addition, changing life style, exercise and using herb and vegetables producing natural antimicrobials are vital issues to be encouraged and investigated in medical research. Last but not least it is vital issue to investigate variations in molecular DNA and relate such variations to metabolic rate, effectiveness of sebaceous and sweat glands secretion as well as variations in their contents.

4- Focus on immunogenetic polymorphisms as well as molecular genetics variations at DNA level for the cytokine, antimicrobial substances and phagocytic activity associated with healthy individuals and that of inflammatory responses.

5- Encourage pharmacogenomics research to correlate variations in molecular biochemical genetics in responsiveness to different drugs, as this issue promises to make prescription of drugs a much more individualized affair in the future.

6- It is important to assess the relative contribution of heritable versus non-heritable factors in disease resistance/susceptibility.

7- Human tissue culture technique should be focused on in the future of medical research. By such technique one can investigate resistance and/or susceptibility to chemicals and disease infection. Impact and applicable results can be secured through well design experiments using virus, bacteria and/or chemicals on tissues inoculated (growing human cells in vitro) of various healthy people to follow up controlling growing condition and observing changes occurred and any abnormalities during experimental period.

8- It is recommended that multidisciplinary team (pharmacists, molecular biologist and pathologists) should work together in drug industry with a focus on biopharmaceutical products manufacturing and evaluation.

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