

Role of Immunologists in the Development of Health Care System

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Role of Immunologists

The role of immunologists in the development of health care of a nation cannot be fully appreciated, unless we look carefully into the history of immunology. The beginning of "Immunology" started in 1798, when Edward Jenner, a county doctor in Gloucestershire, England, UK observed and discovered that milk maids who suffered from cowpox were secure from, and immune to, the future infection of smallpox. He reported 16 cases of resistance to smallpox in farm workers who had recovered from cowpox.

In fact on 14 May 1796, Jenner deliberately inserted "matter taken from a sore (cowpox) on the hand of a dairymaid into the arm of a 8-year-old boy by means of two superficial incisions, barely penetrating the cutis, each about half an inch long." Two months later, Jenner inoculated the same 8-year-old boy with matter from a smallpox patient, the process called "Variolation". However, the boy did not develop smallpox, rather developed a small sore at the site of inoculation. The exposure to the mild disease 'cowpox' had made the boy resistant (immune) to the deadly disease 'smallpox'. In this manner Jenner began the 'Science of Immunology', i.e. the study of the body's response to foreign microbes and substances. The modern terminology of 'Vaccination' is thus derived from 'Vacca' meaning 'Cow'. Subsequently, many investigators and scientists contributed in the development and finally establishment of 'Immunology' as an important biomedical science such as Louise Pasteur, Elic Metchnikoff, Robert Kock, Von Vehrering, Jules Bordet, Paul Erlich, Karl Landsteiner, Astrid Fargraeus, Neil Jerne, Macfarlane Burnet, Peter Medawar, Rodney Porter, Gerald Edelman, Henry Claman, Peter Doherty, Rolf Zinkernagal, Cesar Milstein, Georges Kohler, Susumu Tonegawa and many others [1,2].

Many of the biomedical scientists have received Nobel Prize in different years for their discoveries and contributions in the field of Immunology. Many of their findings and principles were widely applied for diagnostics, therapy and follow-up of patients in a wide range of diseases such as infectious diseases, autoimmune diseases, inflammatory heart diseases, skin diseases, cancers, etc. [3]

The concept of differentiating lymphocytes into T (CD3+,CD4+,CD8+) cells, B (CD19+,CD23+) cells and natural killer (NK) (CD3-,CD16+) cells laid the foundation stone for modern

immunology strongly. The establishment of hybridoma technology in 1975 for production of monoclonal antibody (MCA) has contributed immensely to the speedy development of modern immunology and thus applications in modern medicine and laboratory medicine [4,5]. Further, Mosmann and Coffmann characterized the functional and phenotypic diversity of CD4+ T-cells into Th1 and Th2 cells based on production of cytokines, i.e. interferon- γ interleukin-2 (IL-2), interleukin-4 (IL-4), etc. The Th1 and Th2 cells exhibits critically different effector mechanisms in host defenses against infections such as Mycobacterium tuberculosis, resulting in drastically different outcomes [6]. In the decades since, the Th1/Th2 model has come to predominate investigations of immunopathological diseases and host defense to infectious pathogens. The diversity of these CD4+ T-cells has gained appreciation in recent years, with important applications for autoimmunity, inflammatory disorders, cancers, etc. [7,8]. Many disease models in animals were developed for studies implicating IL-4, IFN- γ , IL-12 and TNF- α and importantly, in patients with myocarditis or idiopathic dilated cardiomyopathy (ICMP) and rheumatoid arthritis having conflicting outcome [8,9]. Soon other subsets of CD4+ T-cells such as Th17, Th22, etc. have been characterized and implicated in disease processes [8]. Among these subsets, Th17 cells have been implicated in myocarditis, rheumatoid arthritis, etc. The cytokine IL-17 under the influence of TGF- β , IL-12, IL-23, etc., was reported to be important for the immunopathogenesis of these diseases [8-12]. In addition to TNF- α , IL-17 has become a very important therapeutic target in these diseases [9-14]. Recently, major advances have revealed that B-cells and its subsets such as CD5+, CD19+, CD22+, CD23+, etc. serve extraordinarily diverse functions within the immune system in addition to antibody production. These functions contribute to breakdown of immunological tolerance leading to autoimmunity and receptor editing is also essential to prevent autoimmune disorders. Both abnormalities in the distribution of B-cell subsets and the benefits of ablative B-cell therapy of autoimmune states confirm their importance. Specific autoantibodies are widely used for diagnosis of autoimmune diseases such as systemic lupus arethematosus (SLE), rheumatoid arthritis (RA), thyroid diseases, etc. in immunodiagnostic laboratories for the last many years. These findings have opened new prospects for immunotherapy of autoimmune diseases and further studies in humans as well as in animal research models [15-17].

Certain cancers can use inflammatory mediators for their own benefit to induce angiogenesis and tissue remodeling. For example, it has been demonstrated that in non-small cell lung carcinoma, IL-17 can promote tumour growth through the enhancement of angiogenesis – mediating factor production such as IL-23 [18-20]. In contrary, it was reported that IL-17 production can inhibit tumour cell growth due to recruitment of CD8+ T-lymphocytes and production of IFN-gamma with cytotoxic activity against the tumour [21,22]. Although the role of inflammation in cancer, remains a controversial issue, these reports suggest that Th17 cells might have an important contribution in the field of cancer immunology which needs further studies [7].

Skin is the biggest organ of the body and almost all dermatological diseases have immunological implications such as Psoriasis, Atopic Dermatitis, etc. Many reports have identified the presence of high levels of Th17 and Th1 cytokines in psoriatic lesions [23]. Different treatment modalities are currently being developed for psoriatic patients such as with etanercept (TNF- α signaling blocker), cyclosporine (immunosuppressive agent), etc. These treatments lead to reduced expression of IL-17, IL-22, IFN-gamma to baseline levels and also, other proinflammatory cytokines such as IL-8, IL-1beta, IL-6, IL-23 [24,25]. These observations clearly demonstrated a crucial role of these cytokines in the immunopathogenesis of Psoriasis, a prominent skin disorder [24,26]. Atopic Dermatitis, another important skin disorder, has been implicated with various pathogenic mechanisms including genetic factors, neuroimmunological factors, skin barrier dysfunction and immunological mechanisms [27-29]. Among these mechanisms, the molecular events and pathways for the pathogenesis of AD were predominately geared to immunological facts and accordingly, integrated into a hypothesis reported by Guttman - Yassky et al. [6,28] Despite its increasing prevalence worldwide, and the burden on society, specific therapies for AD are still limited, and most commonly used therapies are not based on a scientific mechanistic understanding of pathogenesis [6-8]. One might hypothesize that, similar to psoriasis, epidermal reaction may be largely restored to normal with selective immune suppression. A recent study of AD patients that were treated with narrow band (NB) UVB therapy, showed that reversal of clinical disease activity was associated with reversal of the epidermal pathology including reduction in epidermal thickness and expression of proliferation markers [29]. As the new insights into the immune and molecular pathways of AD increase, a variety of experimental agents, particularly biological agents that target pathogenic molecules bring promise of safe and effective therapeutics for long term use. Interestingly, some of the emerging and most promising biological therapies that are in development or in clinical trials are stated below: Barrier repair, Allergen specific immunotherapy, targeted immunomodulating therapies (Anti-IgE therapy, Anti-CD20, Inhibition of T-cell responses, Th2-cell inhibition strategies/Anti IL4-therapies, Anti IL-5 strategies, Anti IL-31, Targeting TSLP), Targeting Th22, Targeting Th17/IL-12/IL-23 pathway, Recombinant IFN- γ , Anti IL-6R, Anti TNF agents, Phosphodiesterase inhibitors, AR-gamma agonists. However, further developments in future targeting and

inhibiting cytokines, chemokines and signal transduction are strong possibilities [28-35].

In consideration of the above stated background it can be assumed that Immunologists have a great role to play in the development of health care system in all countries of the world. The role of Immunology, and hence the Immunologists, in this sector in any developing country including Bangladesh can be accomplished provided the governments act appropriately. For Bangladesh, to this end, we recommend the following: (i) Diagnostic Immunology Laboratory to be set up in every Rural/Upazella Health Complex with a number of routine and specialized immunodiagnostic tests. This would immensely help the rural population in terms of saving money and time and botheration of travelling to district level laboratory services; Secondly, it will definitely help employment of qualified medical/health technologists and junior doctors and availability of them at the rural/Upazella level; (ii) Biomedical research laboratories to be set up at district level to build up research capacity in immunological field in developing countries also like Bangladesh. This will help to engage/employ best quality medical and biomedical graduates and utilize their talents for discovery of new facts relevant to immunopathogenesis, immunodiagnosis, immune-interventions (treatments) and follow-up of patients suffering from diseases with immunological implications.

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