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The evolution of clinical immunology and allergy in Australia

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HISTORICAL PERSPECTIVE

In this, the 50th year of the formal promulgation of the Clonal Selection Theory, it is appropriate to reflect in broad terms on the impact Burnet and Fenner's[1,2] work has had on Australian Immunology. Not only did Clonal Selection provide the overall framework for the adaptive immune system, but here in Australia it also established immunology as one of this country's enduring strengths in medical science. It, therefore, comes as no surprise that the clinical specialty of immunology and allergy has flourished as an offshoot of Burnet's legacy, in parallel with the evolution of the more basic aspects of the joint discipline.

The beginnings

Given the location of the Walter and Eliza Hall Institute of Medical Research, it was to be expected that the first two clinical units formally established during the 1960s would be sited in Melbourne, one at the Hall Institute itself under Dr Ian Mackay, the other at the Alfred Hospital under Professor Richie Nairn. At that time the former was more clinically orientated with the focus on autoimmune liver disease, while the latter dealt more directly with immunopathology. Their creation coincided with much interest in the field overseas in both Europe and the United States of America.[3,4]

Interestingly, allergy clinics preceded these units by some 30 odd years and were located at the Alfred Hospital (separate from Nairn's department) in Melbourne and Royal Prince Alfred and Royal North Shore Hospitals in Sydney. As a result the first formal clinical body to be registered was the Australian Society of Allergists in 1953, which 10 years later became the Australian College of Allergists incorporated under the auspices of the British Medical Association (Australia) and then the Australian College of Allergy. The College remained separate from the Australian Society of Immunology established in 1970 and included a diverse range of medical practitioners as well as scientifically trained graduates.

Thus, early on clinical immunology and allergy were seen as distinct entities, a trend that has persisted in other parts of the world, albeit not here.[5]

Maturation

The controversy over the relationship between clinical immunology and allergy was never more apparent than in the United Kingdom as was their role in internal medicine and are worth discussing here as some of the issues are still pertinent to this day. As late as 1981 Professor AM Denman wrote an article entitled 'What is Clinical Immunology?'[6] in which he recorded the responses of five senior physicians to questions relating to 10 clinical case histories of patients with immunological and allergic diseases. Their responses as non-immunologists led him to draw the following conclusions: 'clinicians regard immunology as a form of clinical practice based on the laboratory' and 'it is more economical and convenient if existing departments of clinical pathology incorporate standard immunological techniques in their working programmes'. The Denman article then formed the basis of a *Lancet* editorial[7] which stated that:

'The specialty is here to stay, but whether the orientation will be laboratory or bedside is not yet clear. No doubt many clinical immunologists like many haematologists would opt for a foot in each camp, but it would seem that their colleagues in other specialties take a different view: they would confine the clinical immunologist largely to his laboratory and would keep their hold on the day-to-day management of immunological problems'… 'one thorny related problem is the question of allergy. Should it be a separate specialty or should the existing system continue?'… 'Until clinicians with an interest in allergy can present a more united front, there may be difficulties in persuading outsiders that allergy qualifies as a specialty'.

The response to this editorial from Professor JF Soothill, a doyenne of paediatric immunology and allergy is as interesting as it is provocative:[8]

'Sir, there is a fundamental non-sequitur in the last sentence of your June 27 editorial: 'until clinicians with an interest in allergy can present a more united front, there may be difficulty in persuading outsiders that allergy qualifies as a specialty'. It is the shocking mess that physicians with a superficial and casual interest in allergy have achieved in the management of these the commonest chronic diseases which points to the need for care of such patients by doctors competent to look after them. Naturally we do not expect the amateur and incompetent to share this view, but dissatisfaction with current care has been one of the factors leading patients (and, more importantly, the parents of affected children) to consult cranks, quacks and even commerce'.

Soothill went on to add 'I feel sure that clinical allergy is a branch of clinical immunology' and 'my main concern is that we not have clinical immunology as an exclusive laboratory discipline'.

In this country, by contrast, the early 1970s saw the rapid expansion of clinical immunology units to other States based on the Mackay

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and Whittingham model,[9] initially in New South Wales[10,11] and Western Australia followed over the years by South Australia, Queensland, Tasmania, Australian Capital Territory and also New Zealand. This rapid expansion coincided with recognition of immunology by the Royal Australasian College of Physicians and the Royal College of Pathologists of Australasia (RCPA) as both a clinical and a pathological specialty in 1973.

The outcome was creation of three diplomas, one each in immunopathology and clinical immunology and the third (and most popular) a 4-year diploma from both colleges. A Joint Specialist Advisory Committee was established to oversee the required training programmes and a Chief Censor in Immunology was appointed by the RCPA. A key decision was made early on, given the rapid development of the scientific basis of both clinical immunology and allergy, to bring the two related subjects together within the diplomas and associated training programmes. This was most important on three counts: first, it provided a 'home' for allergy in specialty medicine; second, it ensured that a start could be made in dealing with the great shortage of practicing allergists in this country; and third, it meant that specialty training became available for paediatricians interested in this combined field who have to deal with important conditions like immunodeficiency states and fatal anaphylaxis. The linking of allergy with clinical immunology within the Colleges' diplomas has been unique to Australia, which in my opinion now has a better training system than either the United States of America, United Kingdom or other countries in Europe. As a consequence of this, recruitment of trainees has been sustained over the years resulting in maintenance of high-quality clinical service units at hospitals and an expansion in well-qualified clinical allergists.

The rapid evolution of clinical immunology and allergy led in 1983 to the creation within the Australasian Society for Immunology (ASI) of the Clinical Immunology Group (CIG). This important initiative in turn was the forerunner of the Australasian Society for Clinical Immunology and Allergy (ASCIA), which was established in 1991 by amalgamation of the Australian College of Allergy with the CIG of ASI. At the time I recall that the placement of clinical immunology before allergy in the title was agreed to by one vote! ASCIA has flourished ever since and has played a central role in development of these disciplines within Australasia.

The existence in the 1980s of a strong clinical immunology sector in Australian medicine had one other important outcome. When human immunodeficiency virus (HIV)/AIDS emerged, the existence in most states of dual clinical and laboratory service–based units meant that a well-trained workforce was available to combat this new challenge. Consequently, a number of clinical immunology units began to care for HIV/AIDS patients, a trend which has led to healthy cooperation between immunologists and infectious disease physicians. Thus, at some hospitals, resident staff rotate between the two services and patients are triaged out of Accident and Emergency to whichever service is on call at the time.

Service cooperation has also extended to rheumatology at hospitals like Royal Prince Alfred in Sydney, for example and rotations through clinical immunology/allergy departments for trainees from a range of other disciplines (for example haematology, respiratory medicine, gastroenterology, oncology and molecular medicine) have been a feature of several of them over the past 30 years. Quite apart from the obvious benefit to the trainees from the other disciplines, a positive outcome for our departments has also occurred in the sense that a steady flow of postgraduate students has joined the associated research laboratories for their PhD's. Consequently there is now a cadre of well-trained specialists in those disciplines who care for a range of patients with immunopathic diseases and only rarely need to consult the immunologically based specialist (see section 'The role and identity of the immunologist/allergist in clinical medicine' and Table 1).

THE ROLE AND IDENTITY OF THE IMMUNOLOGIST/ALLERGIST IN CLINICAL MEDICINE

Past experience

None other than Sir Peter Medawar was prepared to say at a Royal Society Symposium on 'Clinical Immunology and the Physician' held in 1974 that Immunology 'bears upon every branch of medicine and upon the performance of every organ in the body'. This statement as it pertains to disease pathogenesis (and to some extent diagnosis) is clearly valid. Thus, the opinion of a specialist immunologist has traditionally been and still is in high demand at grand rounds when the diagnosis is uncertain or the word 'idiopathic' creeps into the discussion. On the other hand, it is interesting to note that many of the practical advances of the early years (1960–85) of our broadly based discipline were made largely by non-immunologists, either serendipitously or inspired by clinical expediency. I am thinking here of such procedures as renal transplantation before the era of routine tissue typing, development of anti-

Table 1 SWOT analysis

Strengths	*Weaknesses*
• Burnet inheritance: research base • Relevance to multiple diseases • Multiple applications • Strong clinical departments with associated research labs/centres • Superior training programmes • HIV/AIDS link • Relevance to developing as well as developed world	• What is an immunological patient? • Limited involvement in monoclonal Ab/cytokine clinical trials • Limited research consortia/networks
Opportunities for	*Threats from*
• Allergy practice • Greater involvement in vaccinology (positive and negative) • Analysis of IVIG mechanisms • Surrogate marker development e.g. for memory • *Cell therapy, e.g. with* Treg CD8 T cells DCs • Studying the human immune system which differs significantly from that of rodents • Biotechnology development	• Rotating trainees from other disciplines • Automated diagnostic instruments • Loss of multidisciplinary clinics • In research, the increasing complexity of the immune system and its control

Abbreviations: AIDS, acquired immune deficiency syndrome; DC, dendritic cell; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin.

RhD therapy for treating Rh disease of the newborn in 1965 and the later use of pre-transplant blood transfusion to promote allograft survival—all instituted successfully without being based on established immunological principles. Perhaps one exception to this trend was the widespread use of desensitization by clinical allergists including treatment by the sublingual route, unscientific at that time but now seemingly effective in some situations for which a sound immunological explanation exists.

What did the specialist immunological community have in its clinical toolbox at the time? Clearly, the diagnostic services some of which specialized in tissue typing and development of leukaemia/lymphoma markers played a significant role in firmly establishing the fifth specialty in pathology. On the clinical front, by contrast, we had less to offer. There was Sherwood Lawrence's transfer factor, a low molecular weight (<10 kDa) leucocyte extract that attracted a great deal of interest because it could apparently induce antigen-specific T-cell immunity. It was used to treat patients with T-cell immunodeficiencies like autoimmune polyendocrinopathy candidiasis ectodermal dystrophy[12] and multiple sclerosis[13] where it appeared to be beneficial despite, in retrospect, lacking any known cytokines. Like the original suppressor T cells, it vanished from the clinical arena in the early 1980s, never to return (in contrast to the re-emergence of suppressor T cells in the guise of Tregs). Over the same period, trials were undertaken with non-specific adjuvants like Bacillus Calmette-Guérin (BCG) and *Corynebacterium Parvum* in patients with leukaemia and solid tumours, but with minimal long-term benefit. In 1975, Kohler and Milstein[14] published their seminal paper on murine monoclonal antibodies, but it took 10 years for the first potentially encouraging trial to be completed in humans. Following refinements in the technology by molecular immunologists such as Sir Gregory Winter,[15] the number of approved antibodies has risen exponentially to the stage where 50% of new drugs approved by regulatory authorities like the Food and Drug Administration are now monoclonals or comparable fusion proteins (Figure 1).[16] However, they are often used in combination with other therapy (for example anti-tumour-necrosis factor (TNF) inhibitors with methotrexate)[17] and the trials have usually been performed by non-immunologists.

In a sense our contributions to patient management in the 1960–85 era were summarized by a rare witty respiratory physician when, at grand rounds, he defined an immunological approach to treatment as follows: 'if you can't suppress it (with steroids/cytotoxics) and you can't remove it (by plasmapheresis), then stimulate it'. Perhaps still partly true today with the addition of: 'replace it or modulate it', if one thinks about products like intravenous immunoglobulin (IVIG).

Current situation

Clinical Immunology/Allergy, given its widespread relevance to diagnosis and treatment of a range of diseases, has earned the title of the 'cancer of medicine' and the 'last bastion of general medicine'. But how do we respond to the rhetorical question posed by our cynical colleagues from other specialties when they ask: 'What is an immunological patient?' and of course do not wait for an answer. Hopefully, that attitude will change following the recent anti-CD28 phase 1 trial when immunological expertise was only sought late in the piece.[18] Nevertheless, it does highlight the issue of our clinical identity. One way of tackling it is to undertake a **S**trengths, **W**eaknesses, **O**pportunities and **T**hreats (SWOT) analysis (Table 1). On perusing the strengths, weaknesses, opportunities and threats facing our discipline, the solution is clearly not more of the same; rather it is one of subtle reinvention and capitalizing on the veritable explosion in translational immunology and allergy over the past 5–10 years. Among the recent advances of significance is the demonstration of an increasing number of differences between the human and mouse immune system, the application of which to clinical practice should be the province of the trained clinical immunologist/allergist with a research bent (Table 1).

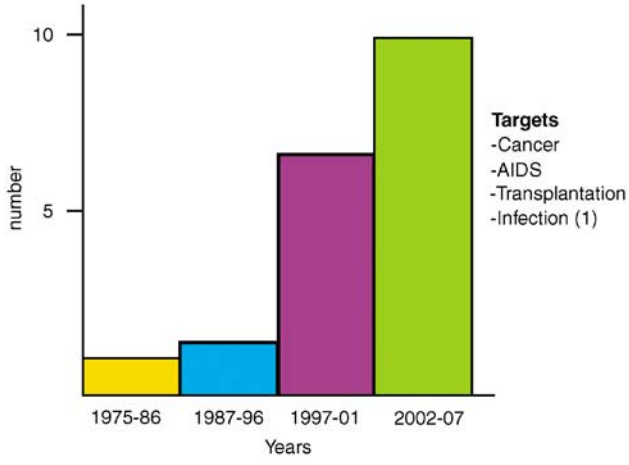

Figure 1 Exponential rise in monoclonal antibodies (mAbs) approved for clinical use. Now 50% of new drug approvals are for mAbs or equivalent fusion proteins.

Table 2 Crystal-ball gazing and future priorities in clinical immunology/allergy[19]

No.	*Priority*	*Type of communication*
1	Cells	Between cells of immune system (leucocyte-centric axis)
	DC⇔T cell axis	
	Tregs vs effectors	
2	Tissue reactions	Between tissues and cells of immune system
	Inflammation	
	Remodelling	
	Repair	
3	Genomes	Between genes
	Recessive mutations in immune cells[21]	
	Polymorphisms and disease susceptibility	
	rDNA and plasmid vaccines	
4	People	Between
		Scientists and clinicians (network, consortia)
		Scientists/clinicians and community

Abbreviation: DC, dendritic cell.

FUTURE PROSPECTS

Scope

Our toolbox is now constructed from a much more sophisticated Burnetian framework and contains an array of powerful technologies (for example flow cytometry, panels of well-characterized monoclonal antibodies, microarrays and so on) which together with the strengths and opportunities outlined in the SWOT analysis (Table 1) put us in a much better position to identify targets for clinical research, therapy and practice. A good starting point is an article published in 2006 entitled 'Crystal-ball gazing—the future of immunological research viewed from the cutting edge'.[19] In this a number of experts well known to most of us gave their views on the scope of clinical immunology/allergy in the future. In synoptic terms, this revolves around the concept of communication with and between cells and people (Table 2). By way of illustration, it is worth highlighting four issues raised in the article. The first is the crucial role played by cross-talk between dendritic cells (DCs) and T-cell subsets including Tregs. Herein lies the basis of the 'hygiene hypothesis' that is relevant to the pathogenesis of autoimmune and allergic diseases. What is the real explanation for the inverse relationship (if it is indeed such) in the developed world between the decline in incidence of serious infections on the one hand and the rise in incidence of autoimmunity and allergy on the other?[20] The jury remains out and the question in practice will need to be solved by the human immunologist/allergist.

Second, there is the issue of the tissue reaction to immunological insults. When looking at developing novel modalities of therapy, a strong case is made by several contributors to the article for focusing on tissue inflammation, remodelling and repair rather than just the immune system *per se*, given the intimate relationship of innate immune responses to the tissue microenvironment. Third is the matter of communication within genomes, manifested in humans by recombination and interaction between recessive genes that collectively lead to the common polygenic immunopathic disorders.[21] Herein lies clues to disease susceptibility and its association with polymorphisms in immunologically important genes like those encoding surface receptors (for example FcR, MHC class I-III) and signalling molecules (for example AIRE, SAP).

Finally, attention is drawn to the need for communication between scientists and clinicians and between both of them and the public: with respect to communication with the general public, patient support groups and politicians, the two most recent successes overseas have been Research America and the United Kingdom based Academy of Medical Sciences the brainchild of Sir Peter Lachmann, a contributor to the crystal-ball gazing article, and a very effective lobby group. The equivalent organizations here, namely Research Australia and the Australian Society for Medical Research therefore deserve strong support although one might ask whether we would also benefit from an Australian version of the Academy of Medical Sciences. In the case of communication between scientists and clinicians, the European countries in particular have excelled in the development of networks and consortia supported by data and tissue banks, whereas here only limited progress has been made (Table 1). The ASCIA immunodeficiency register that operates at the national level is an excellent start as are recent initiatives by MS Research Australia, but we still lack the overall capacity to study orphan diseases like the various lupus syndromes, other systemic autoimmune disorders and anaphylaxis particularly in children. If clinical immunologists/allergists are to play a significant role in the future development of both new diagnostics and therapeutics, then the barriers need to come down between states, hospital departments and research centres, particularly in a small country like Australia. In this regard we could learn from the oncologists as well as those of our colleagues focusing specifically on HIV/AIDS.

Challenges and priorities

In his Croonian Lecture of 1901, Paul Ehrlich enunciated his vision for what in practice is 'immunotherapy' in this broad sense of the term:[22]

'It is hoped that immunizations such as these, which are of great theoretical interest, may come to be available for clinical application attacking epithelial new formation, particularly carcinoma by means of specific anti-epithelial sera… I trust, my Lords and gentlemen, that we no longer find ourselves lost on a boundless sea, but that we have already caught a distinct glimpse of the land where we hope, nay, we expect, will yield rich treasures for biology and therapeutics'.

The glimpse of the 'land of rich treasures' he refers to has without doubt become a reality in the past decade. This is not only due to the clinical efficacy of monoclonal antibodies (Figure 1), but to a much clearer understanding of how the human immune system is regulated, based of course on the original Burnet's clonal selection theory. Although Tregs (neé suppressor T cells) have once again become a somewhat poorly controlled bandwagon, the ground rules are in place for designing rational approaches to switching immune response off as well as on.

For convenience, one can think of 'immunotherapy' within the framework outlined in Table 3 under the three headings of antigen, cell and antibody-based (cytokines will continue to play an adjunctive role). In each case the ultimate goal, however, is the same, namely to generate a long-term 'memory' effect. The challenge for the vaccinologist is to develop better adjuvants (alum is the only one approved for clinical use) and surrogate markers for T-cell memory; while for the therapists it is to achieve selective and prolonged inhibition of unwanted responses. Blockade of effector mechanisms with IVIG or defined monoclonal antibodies (for example to TNF, CD3, CD20) has proven increasingly effective in autoimmune diseases and allograft rejection. On the other hand the benefit is transient and repeated administration is required. The same applies to desensitization in allergic disease. Thus, the next step is to devise ways of achieving prolonged and selective inhibition of pathogenic responses (for example via cross-linking of FcγRIIb and BCR with antibodies or antibody mimics) or of safely activating Tregs with memory characteristics;[23] the latter goal may well be achieved in transplantation before the immunopathic and allergic disorders. Interestingly, the converse strategy of removing tumour-infiltrating Tregs with cytotoxic drug regimens is showing promise[24] and could be incorporated into oncological practice earlier than 'positive' cell therapy with tumour peptide pulsed cytotoxic $CD8^+$ T cells or DCs which remains a real challenge in terms of quality control and practicality. Long-term therapy based on immune deviation and shifting responses from Th1 to Th2 (or *vice versa*) is less desirable since polymorphisms in disease susceptibility genes may interfere with efficacy and unwanted side effects may take months or even years to manifest (for example induction or autoimmune haemolytic anaemia late after 'curing' NOD mice of type I diabetes with BCG).[25]

Immunotherapy does, however, have a role particularly in the case of mono- and polyclonal antibodies. Here, one of the priorities is to define the mechanisms of the immunomodulatory action of IVIG, given its costs and high frequency of use. Indeed the number of diseases where it is being used in an attempt to modulate immune responses has risen to 35,[26] making IVIG more popular than corticosteroids and aspirin combined. Without knowing the mechanism of action in

Table 3 Framework for immunotherapy

Category	*Examples*	*Route*	*Possible mechanisms*	*Outcome (+/–)*	*Clinical examples*
Ag based	Peptide/protein	s.c./i.m.	Protective response	+	Vaccination
	(± Adjuvant)	Mucosal	Protective response	+	Vaccination
				–	De-sensitization in allergy
	'Naked' DNA	Intradermal	Protective response	+	Vaccination
	DNA-containing vectors	Intraportal	T-cell tolerance	–	Xenotransplantation
					Gene therapy
Cell based	Peptide pulsed $CD8^+$ T cells	i.v.	Protective response	+	Tumour therapy
	Peptide pulsed				
	Mature DC	s.c.	Protective response	+	Tumour therapy
	Immature DC	s.c.	(tolerance via Treg ⇑)	–	Autoimmunity
	B cells	s.c.	(tolerance via Treg ⇑)	–	Autoimmunity
	Tregs	i.v.	Restoration of tolerance	–	Autoimmunity/allotransplant
	Removal of Tregs from tissue	—	Protective response	+	Tumour therapy
Antibody based	Polyclonal vs microbes	i.v./i.m.	Passive protection[a]	+	Systemic infections
	RhD	i.m.	Passive protection	–	RhD disease of newborn
	Pooled (IVIG)	i.v.	Anti-inflammatory effects	–	Autoimmune and vascular inflammatory diseases
			Restoration of tolerance		
	Monoclonal	i.v./i.m.	Mediator neutralization	–	C'/cytokine-dependent diseases
			Cell death	–	Lymphoma therapy

Abbreviations: DC, dendritic cell; i.v., intravenous; IVIG, intravenous immunoglobulin; i.m., intramuscular; s.c., subcutaneous.
[a]Hyperimmune IgG to varicella zoster, CMV and so on.

the majority of diseases being treated, the opportunity for substituting monoclonals or other immunomodulators is very limited. On the other hand, hyperimmune polyclonals or cocktails of monoclonals will continue to be needed particularly where there is a mutating target as in viral and parasitic infections or tumours.[27]

The increased availability of novel immunotherapeutic stratagems raises one final issue that is worthy of discussion, namely where should our priorities lie given the enormous potential of applied immunology on the one hand and the substantial costs associated with taking such treatments into the clinic on the other. Should we, for example, be focusing on maintaining the well-being of the elderly in developed countries like Australia or should we be concentrating on the young of the developing world whose lifespan remains so short in relative terms? The spontaneous reaction of at least a significant proportion of us, I suspect, is to favour the latter target. However, the hygiene hypothesis tells us that an effective vaccine against major infections like malaria, HIV and TB could have two outcomes: initially a dramatic rise in populations with the risk of greater poverty and malnutrition, followed later by a rise in the diseases of developed countries like autoimmunity and allergy (Figure 2); a difficult choice, both ethical and scientific, but one with which the community of clinical immunologists and allergists need to grapple. Let us hope that the addition of 'negative' to 'positive' vaccination will go at least some way to solving this dilemma.

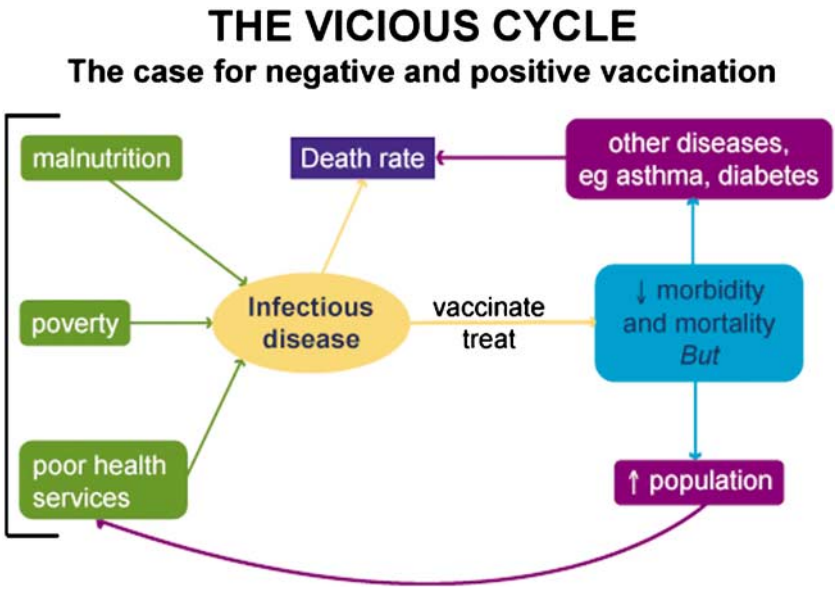

Figure 2 The vicious cycle: outcomes of potential advances in vaccinology in the developing world.

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