Clinical and Experimental Immunology SPECIAL REVIEW doi:10.1111/j.1365-2249.2006.03234.x

Marking the 50th Anniversary of the British Society for Immunology

Crystal-ball gazing – the future of immunological research viewed from the cutting edge

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Introduction

The concept of gazing into crystal balls to view the future is not something immunologists are particularly prone to do; it is better left to psychics, quacks and astrologers. We are more likely to spend our time looking back, scouring the literature for precedents or clues to explain our latest findings. Yet the 50th Anniversary of the British Society for Immunology (BSI) offers an opportunity to both reflect and look forward. As a means of achieving this we asked leading immunologists, each of whom made their mark in this field in the preceding half-century, to speculate on what the next 10, 20 or 50 years might hold. As you will read for yourself, their attempts at clairvoyance provoke considerable thought and controversy.

I had engaged in some ball-gazing myself, but in my case I tried to predict what our sages and seers might write. Vaccines and regulatory T cells were high on my list as key elements of the future, although it was hard to be sure precisely how the arguments would fall out. In the end, there is consensus that vaccines, one of the success stories of the past, will continue to unlock cures to disease in the future. On the other hand, regulatory T cells feature as both a benign and malign influence. Well, at least that means that one of our clairvoyants will be right! There seems to be consensus that new technologies and the application of non-immunological modalities, such as systems biology, will emerge as being important to our future. The importance of engagement of the non-scientific community in what we do is also emphasized as a key to future success. There is even some 'immunosophical' discussion of disease mechanisms that may enhance such dialogue. Finally, and somewhat disappointingly for me at least, none of our oracles described the immunological equivalent of 'you will meet a tall dark stranger' – but surely there will be some surprises in the next 50 years?

MARK PEAKMAN
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Ts (or T_{reg}, if you prefer) will inherit the earth

Leslie Brent

It was R. K. Gershon who, in the early 1970s, discovered T cells that had the power to suppress the response to soluble antigens by other T cells. He described his data in terms of 'infectious tolerance', as he could transfer tolerance adoptively with suppressor T cells (Ts). My team at St Mary's Hospital was the first to show that this was equally true for alloantigens. Thus, spleen T lymphocytes taken from mice made specifically tolerant in adult life to allogeneic skin grafts transferred the tolerance to normal mice given a brief course of anti-lymphocyte serum without previously having encountered the alloantigens.

While one would have thought that our evidence had been incontrovertible, molecular immunologists were sniffy, not to say dismissive, about Ts because at that time we did not have a specific profile for this subpopulation of T cells, and Ts (and those who worked with them) were given a hard time of it for many years. Now that they have been resuscitated as

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T_{reg}, with a distinct phenotype, they are back in vogue again and, indeed, the subject of extensive investigation not only in the field of transplantation but also in autoimmunity, infection and other areas.

My crystal ball tells me that Ts (or T_{reg}) will lead us to the Holy Grail so far as clinical tissue and organ transplantation is concerned. There is already some promising experimental and clinical work being conducted at Kiel University on the *in vitro* induction of donor-specific Ts and I believe that, although there are other approaches to the induction of clinical tolerance, this strategy is by far the most persuasive and holds out the greatest hope of banishing immunosuppressive drugs from clinical protocols.

The results in clinical organ transplantation, using drugs and anti-thymocyte globulin, are now so good that it demands great courage and even daring for transplant surgeons to embrace new and untried protocols. Yet we know that, using immunosuppression, there is a steady attrition in graft survival, and the side effects can be a heavy price to pay for the survival of a transplant. I believe that tolerance induction with protocols that generate T_{reg} *in vitro* or *in vivo* will provide the quantum leap forwards for which we have all been waiting.

The next 50 years

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Congratulations to the British Society for Immunology on its 50th Anniversary. This past half-century of immunology has been successful in dismantling the immune system into its component cells and molecules. The coming decades, I believe, will be marked by reconstruction, by synthesis of the immune system as a system. It is now clear to all that immune behaviour is not determined by isolated clones, each oblivious of its brethren. On the contrary, immune physiology emerges from the collective interactions of many different types of cells, 'innate' and 'adaptive' together, exchanging information among themselves by cytokines, chemokines and other cell interaction molecules. Indeed, it is now clear that the immune system is in constant dialogue with the body – wound healing, angiogenesis, connective tissue formation, regeneration, pruning, waste disposal and other daily maintenance functions. Now we have to put the dismantled parts together into a working whole; otherwise, we will not achieve understanding and control. Just as lymphocytes and antibodies were key players for life science generally in the era of analytical cell and molecular biology, the immune system will be a key player, the prototypic multicellular system, in the emerging era of synthesis, called by some 'systems biology' (previously called physiology). Objectives, methods and therapies will be approached differently.

Methodologically, we will find ourselves consorting with computer scientists, physicists of complex systems and applied mathematicians. Integrative, dynamic information technologies, including new instruments for real-time imaging, will engage us. We will have to think about immune system information, as well as about discrete cells and molecules. Our best students will have to know more than how to manipulate nucleic acids and proteins; we will teach differently.

Programmatically, we will want to learn how the immune system – as a system – gathers and integrates information about the state of the body, and how it uses this information to make dynamic decisions that regulate reparative inflammation and ongoing body maintenance.

Therapeutically, we will know how to teach the immune system – through knowledgeable vaccinations – to deal more effectively with cancers and grafts, and not only to prevent or resist infectious diseases. Unravelling the physiology of immune regulation will provide new, natural immune regulatory molecules for medicine. Individuals will benefit from immune therapies tailored to individual needs (individualized immune therapy). Immune systems are individualized because we each live in an individual world; now is the time for our collective brains to learn what our immune systems have learned over the past 500 million years. Now is the time to study the immune system and use it, too.

Communicating immunology

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A big challenge for scientists is to communicate the legitimacy and importance of what we do, both to politicians and to the broader, tax-paying public. The rules of evidence and relative risk that we accept are not necessarily the values most people live by. Anyone who monitored the MMR/autism story, or has looked up immunization on the web, will realize that the vaccines we regard as an enormous contribution to human wellbeing are by no means accepted as such by many.

Over the past 10 years I have spent a great deal of time talking about the importance and nature of science in all sorts of locations, from pubs to town halls to parliaments. The questions from the floor can be a major eye-opener. Talk-back radio is an even more 'interesting' experience. Part of my problem with this type of activity is that the exercise seems ephemeral, just so much 'hot air'. Scientists are not journalists, and we like to see at least some sort of enduring product. As much from frustration as anything else, I sat down and wrote *The Beginner's Guide to Winning the Nobel Prize* (2006; Columbia University Press, New York), which is intended as a very general account of science, its history and how it works for a lay audience. One of the many things I learned from this experience of being a geriatric literary novice is that it is hard to explain immunity.

Ask yourself: do you know of a good, readable account of immunity written for a general readership? We have a number of outstanding textbooks, but these are generally too

advanced for those with no background in biology. By default, we give up the field to the diet entrepreneurs and witch doctors who tell people how to 'build strong immune systems'. We fight defensive actions against people who have no understanding of disease processes, but accumulate anecdotal stories that vaccination is somehow dangerous.

Immunity is enormously complex. Visual material works much better than words. It would, I believe, be a great project for an enterprising collaboration between committed scientists, professional writers, illustrators and media people to put together an integrated written and visual account of the workings of the immune system. There are, for instance, superb time-lapse movies of killer T cells doing what they do that intrigue all who see them. A combined electronic and print 'user's manual' of immunology that can be accessed by logging-in to the nearest crystal ball would be widely welcomed.

The next 50 years in autoimmunity: accelerating progress in immunotherapy

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Those of us who have been working in immunology for a long time (since 1969 for me) have seen amazing technological and conceptual changes which have led to a new wave of immunology-based therapies.

Kohler and Milstein's monoclonal antibody discovery of the late 1970s finally reached patients in the late 1990s with a vengeance, in forms including Infliximab [anti-tumour necrosis factor (TNF) for rheumatoid arthritis, Crohn's disease, etc.], Rituximab (anti-CD20 for lymphoma) and Herceptin (anti-HER2 for breast cancer). These new therapies convincingly documented that monoclonal antibodies were not only a scientific success, but also a commercial and therapeutic success, so the biopharma industries began to invest heavily, and now there are dozens and dozens of new monoclonal antibodies in clinical development and trials.

However, this success is relative. There are still no cures. Response rates can be as low as 20%, but rarely > 80% (very early rheumatoid patients) for any of these 'breakthroughs'. Are they really breakthroughs? Again, it is relative, and for the patients responding there is obvious patient satisfaction borne out by quality of life questionnaires, increased survival, etc.

What of the future? The rationing of these drugs by cost must cease. It probably will, as production costs plummet and competition by new companies for a slice of the huge pie (anti-TNF sales were $7·7 billion in 2005); but more relevant is that there is now a clear path to follow.

In rheumatoid arthritis there is ample evidence with all three approved anti-TNF products that combination therapy with methotrexate has a significant amplifying effect on efficacy without compromising safety. However, not all combinations of drugs are either efficacious or safe, and TNF blockade plus interleukin (IL)-1 blockade was neither efficacious nor safe. But it seems likely that much better combinations will be found which will have the desired effect of increasing the percentage of responders, and the degree of response leading to a cure.

Despite the travails of developing orally available competitors to the anti-TNF biologicals, it is very likely that the power of chemistry will resolve that problem within the next 20 years, so the likely combinations will probably not include anti-TNF antibody or receptor on a long-term basis. It will be still useful for a rapid 'washout' of TNF.

This leads me to another prediction. Many cytokines are now known to be good disease targets, e.g. TNF, IL-6, IL-1, IL-15 and IL-12. Many chronic diseases respond, as witnessed by the seven approved indications for TNF blockade. These are: rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, psoriasis and ulcerative colitis. There are many more successes in clinical trials, including sarcoidosis, ovarian cancer, steroid-resistant asthma and refractory uveitis.

What about acute diseases? Proinflammatory cytokines abound in acute diseases, from sepsis, acute respiratory distress, burns, trauma and head injury. It is paradoxical that chronic diseases are now treated routinely with blockade of proinflammatory cytokines such as TNF, but acute ones are not. Surely we will learn how to use our powerful anti-cytokine therapeutics for an increasing list of acute, life-threatening problems, such as acute respiratory syndrome.

I am an optimist, and predict that with the accelerating pace of scientific and medical discovery and technology all the common autoimmune diseases will be curable within the next 50 years. Talented volunteers are needed to ensure that this prediction will come true. I suspect they will be amply rewarded.

It's the TISSUE!

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> The future is uncertain and unpredictable. That is why it is called the future. However, we can think about what would be an ideal future.
> Kaveh Abdi

The fundamental concept guiding immunologists for the last century has been the self *versus* non-self model, which accorded major decision-making powers to the T and B cells (the cells able to make the self–non-self discrimination). Although this idea has begun to shift to the view that immune responses are controlled by cells of the innate immune system, such as dendritic cells, macrophages, natural killer (NK) cells and NK T cells, a critical conceptual step forward still remains to be taken. Both the old and new concepts still regard bodily tissues and organs as passive players, while the innate and adaptive elements of the immune system are perceived to orchestrate the start to finish of an

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immune response. If, in contrast, we understood there to be a continuous life-long dialogue within the body between all immunocompetent cells, be they intestinal epithelial cells or CD4 T cells, we would appreciate immune responses differently.

In health, we would picture the tissue in intimate contact with its outside world, welcoming the mobile elements of the innate immune system to set up house. The progenitors of the tissue-resident dendritic cells and macrophages would come in and settle down to life within the tissue environs, bathed in its unique intrastitial fluids, this intimacy being what gives this tissue site its unique immunological identity (for example, the TGF-β-rich environment of the eye or the gut). In distress, rather than imagining the T cells coming into a tissue in response to an alarm initiated by tissue resident dendritic cells, the tissue sitting passively in its immobility, we could now imagine the preceding events in that tissue: the extracellular elements curling up in gradual disarray; the increasingly disturbed movements of the different cellular elements; cells suddenly exploding or imploding; macrophages scurrying about to clear up the debris; dendritic cells being dispatched to the draining lymph node carrying tissue-specific instructions; capillaries dilating and changing their surface signals to allow the entry of carefully chosen sets of cells; in short, the unique response to distress of a given tissue. Given the amazingly destructive capacity of the cells of the immune system, it is unlikely that a distressed tissue would allow them to enter and wreak wanton destruction. Having spent its entire life performing its function, responding to changes in its environment, growing and developing and changing, why would it now, in its moment of trouble when its very existence and that of the body in which it resides may be in question, cede its *raison d'être* to the influx of immunocytes? Yet in the traditional perception of an immune response, that is what we have tacitly imagined to be the case.

We, the Ghost Lab, believe that the next 20 years will see the beginnings of a shift from the leucocyte-centric view of immunity to an understanding that our tissues, and even our commensal organisms, play a major role in preventing, initiating and terminating immune responses, as well as in influencing the unique effector class chosen for a response at any particular location. Because we have exceeded the word allowance, we give here only two examples of where this view could take us.

Privileged sites

These will 'disappear'. There are times when we immunologists should hold our long-held ideas up to the yardstick of evolutionary selection and ask if they can stand the scrutiny. It is simply unreasonable to think that any tissue could long remain immunologically unprotectable. Being wet, warm and full of nutrients, it would soon succumb to parasitic invasion. Streilein's work on the eye, in fact, shows that it is not 'privileged', but simply a tissue that cannot withstand the destructive effects of a Th1/DTH response, and tells the immune system "don't do that kind of response here". By making TGF-β, vaso-intestinal peptide (VIP) and melanocyte-stimulating hormone (MSH), the eye tells the immune system to make a response with effector molecules (such as IgA) that can clear a parasite without causing massive additional destruction. We predict that the other privileged sites (testis, brain and hamster cheek pouch) will be found to do similar things, as will many other tissues, including gut and placenta. In many cases, as well as communicating directly with the immune system, the tissues will be found to have resident populations of lymphocytes involved in the homeostasis of the tissue, in healing after injury and in communicating tissue-specific signals to incoming leucocytes.

Tumours

Currently, tumour immunology is focused on T cell-centric therapies. For example, adoptive transfer of high numbers of *in vitro*-expanded tumour-specific T cells. With the discovery of new molecules that inhibit or enhance T cell responses (such as CTLA-4 and 4–1BB, and certainly more to come), we foresee that there will be more and more manipulation of the adoptively transferred T cells in order to create large numbers of the 'fittest' tumour-specific T cells: i.e. the strongest, longest-surviving, killers.

However, we think that focusing on T cell biology may not be enough. It is important to also focus on the biology of the tumour itself, especially on the interface between the tumour stroma and immune system cells. As Dvorak said, tumours resemble non-healing wounds. During normal healing, cells divide and new extracellular matrix and blood vessels form. Tumours are thus in a never-ending healing process, and it is in the interest of a healing tissue to prevent the immune system from creating more damage and disruption. The same molecules that drive the healing process and/or the products of such processes are likely to be signals that either inhibit the immune response or shift the effector class away from the cytolytic responses that create more damage (and that can reject tumours) towards less destructive response types. By identifying and manipulating the signals passed from healing tissues to the immune system, we should be able to make tumours more susceptible to the attack of tumour specific T cells.

A spanner in the works

The rise of anti-terrorism policy in the United States and the perceived need for better biodefence methods and vaccines will probably push much fundamental research into second place, to be replaced by genetic and immunological engineering. We hope that the rest of the world will take up and support the fundamental art and wonder of this fascinating branch of biology.

Ghost Lab members

The Ghost Lab members are: Ainhoa Perez-Diez, Akgul Akpinarli, Andriy Morgun, Brandon Reines, Caelin Cubenas, David Usharauli, Eric Bachelder, Kaveh Abdi, Megan Wilson, Natalia Schulzhenko, Polly Matzinger and Tirumalai Kamala.

Asthma: more than an inflammatory disease

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The recognition that asthma is an inflammatory disorder of the conducting airways leading to intermittent airflow obstruction has provided the rationale for its modern treatment with inhaled corticosteroids together with short- or long-acting β_2 adrenoceptor agonists, and these are now enshrined within international and national management guidelines. Based on the premise that T helper 2 (Th2)-type inflammation was responsible for the airway dysfunction of asthma and that most asthma was associated with allergy (or atopy) it has largely been assumed that allergy *per se* was the cause of asthma. Most asthma has its onset in childhood, and undoubtedly atopy and exposure to allergens contribute to differentiation and the persistence of asthma in childhood [1]. However, an important question that remains unanswered is why atopy affects approximately 40% of the population and yet asthma occurs in only approximately 7%. Put another way, what is it about those who develop asthma that leads to the expression of atopy in the lower airways? Later in life new asthma is most frequently non-atopic, and yet the underlying pathology is almost identical to that seen in the allergic subtype. Finally, if allergic inflammation was the cause of asthma, then at its onset in early childhood, regular inhaled corticosteroids sufficient to suppress symptoms should alter the course of the disease. However, two recent studies in 1–3-year-old children at high risk of developing asthma has revealed that 2 years of therapy with regular inhaled corticosteroids has no effect on the natural history of the disease once the treatment is discontinued [2,3].

While the last three decades witnessed more efficacious, safer and longer-acting inhaled corticosteroids and β_2-adrenoceptor agonists, apart from anti-IgE monoclonal antibody (omalizumab) and leukotriene receptor antagonists (e.g. montelukast), we have nothing new to offer patients, especially treatments that target the underlying cause(s) of the disease. For some years the view has been widely held that respiratory virus infections early in life are protective against allergy (and asthma), based largely on epidemiological studies showing differences in the prevalence of allergy when comparing children who spent their early lives in day care centres (e.g. China, Russia, former East Germany) with those who had not. However, this is purely theoretical. Recently, Lemanske *et al*. have shown that exposure to the common cold viruses, rhinoviruses (HRV), sufficient to cause wheezing, is the strongest risk factor for developing asthma even beyond other respiratory viruses [4]. It has long been known that HRV, a usually innocuous virus, is associated with a high proportion of asthma exacerbation, both in adults and children. Recently we have shown that this is due most probably to a defect in interferons-β and -λ production by lower airway epithelial cells [5,6]. In normal individuals invasion of airway epithelial cells by HRV initiates the apoptotic cascade which terminates viral replication and removes the epithelial cell 'quickly' from the airways. However, in asthma this is defective, leading to HRV replication and eventual cytotoxic killing of the epithelial cells. The net result of this is increased viral replication and shedding and release of inflammatory products to initiate an exacerbation. Virus-induced apoptosis of airway epithelial cells is dependent on the production of interferons [5,6].

Could it be that the origins of asthma lie within the epithelium itself? In support of this idea, epithelial damage and airway wall 'remodelling' are present at the onset of asthma in childhood [7]. Other factors associated with the origins of asthma such as environmental tobacco smoke exposure, other air pollutants and allergens all interface with the epithelium. In the case of allergens, it is those with proteolytic and other biological activities that appear to be especially associated with asthma, such as those from house dust mites, fungi and certain pollens [8]. These proteolytic allergens share with respiratory viruses [9] the capacity to degrade tight junction proteins to break down the epithelial barrier, thereby allowing access of other environmental insults to immune and inflammatory cells deep in the airway wall. Further, the fact that the majority of the novel genera associated with asthma and identified by positional closing where no assumptions are made about their function(s) lie in the epithelium [human leucocyte antigen-G (HLA-G), dipeptylpeptidase-related ancillary subunit (DPP10), G protein-coupled receptor for asthma (GPRA), filaggrin, epithelium-specific Ets (ESE)-2 and -3, mucin 8 (MUC8) and AluyMICB), rather than genes in the immunological or inflammatory cascades, makes the case for a key role of the epithelium in this disease. The discovery that asthmatic airway epithelial cells that are differentiated *in vitro* at an air–liquid interface fail to develop fully functional tight junctions, and even in asthmatic biopsies these are incompletely formed [10], suggests that beyond reduced innate immunity, the barrier function of the lower airway epithelium is abnormal in asthma and this is the reason why the disease starts in the first place, and why so many different inhaled environmental stimuli lead to worsening disease. The fact that the pharmaceutical industry (and research in academic centres) has relied almost solely on allergen (antigen) sensitization and challenge models in animals to screen out anti-asthma treatments means that any drug not active on Th2-driven mechanisms would have been excluded, including agents that act directly on the epithelium. Asthma is a chronic disease involving both inflammation and remodelling of the

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airways, with the latter involving activation of the epithelial–mesenchymal trophic unit [11] as part of a chronic wound scenario. A propensity for epithelial injury and delayed or aberrant repair could be the factor responsible for the chronicity of asthma. Therefore, agents that increase epithelial repair or protect the epithelium against environmental insult as shown recently in the case of epidermal growth factor (EGF) for ulcerative colitis and keratinocyte growth factor (KGF) for oral mucositis [12,13] could provide a basis for a new approach to asthma treatment. The recent identification of a filaggrin gene polymorphism that leads to reduced barrier function in the skin being associated with atopic dermatitis eczema [14,15] is another example of how barrier function influences the development of an atopic disease [16]. The finding that inhaled corticosteroids have little or no effect on virus-induced exacerbations of asthma has led to clinical trials with inhaled human recombinant interferon-β. Both KGF and EGF are also highly effective in repairing the tight junction defect in the epithelium as well as increasing its resistance to environmental insult [17,18]. Perhaps such approaches will be the new generation of asthma therapies, targeted more on protecting the lung against the environment rather than focusing solely on suppressing symptoms and inflammation.

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Crystal-ball gazing for the golden jubilee of the BSI

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> Among all forms of mistake, prophecy is the most gratuitous.
> George Eliot, Middlemarch

I believe that immunology will move to becoming, again, a much more integrated subject as it becomes recognized that the divisions into adaptive and innate and into humoral and cellular are devices for facilitating research rather than a reflection of how the system normally works *in vivo*. This will need a reversal of the trend to increasing specialization and fragmentation, and we will need more immunologists in the mould of John Humphrey and the pioneers who founded the BSI 50 years ago!

The immune system's role in combating infections will become increasingly important with the increasing threats posed by emerging and re-emerging disease and by the growth of antibiotic resistance. There will be major advances

in vaccinology using a number of novel approaches. Plasmid vaccines have the great advantage that a single production facility can make a whole range of vaccines and the problem of how to make them more immunogenic will surely be resolved. Vector-based vaccines are also likely to be developed further and currently highly speculative approaches such as dendritic cell vaccines will – or will not – fulfil their potential. Vaccine approaches to non-infectious diseases, such as cancer, allergy prevention, treatment of autoimmune disease and even drug addiction, will continue to be developed – but success in these fields has already been a long time coming.

It seems likely to me that 'cell therapy' using cells differentiated from stem cell lines will be a major therapeutic development of the next 20 years. Immunology will have a vital role to play in this as it is unlikely that the cells used will be completely histocompatible. There will be major efforts directed at overcoming minor histocompatibility differences, developing techniques for developing tolerance – possibly using regulatory T cells, possibly in other ways.

(Almost) certainly, the next two decades will see a great increase in the effective use of monoclonal antibodies as therapeutic agents. Their success is now highly impressive, but the long lag time since they were first discovered shows that taking basic advances to the clinic always takes longer than one might hope.

Regulation, dysregulation and natural selection

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My crystal ball reveals little of the future, but more of the past. I belong to the generation for whom immunology was only just shaking off the shackles that bound it to medicine and beginning to stand on its own feet. The new developments in biology in the 1940s were connected with evolution. My teachers, J. B. S. Haldane, P. B. Medawar and E. B. Ford, taught us that evolution deals not just with the past, but rather with what is going on all round us. That view led me naturally into immunology, as a new chapter in biological science.

The inheritance of disease susceptibility has now become a major theme of immunology. We are watching the unravelling of the contributions made by gene structure (variation in the coding sequences) and by gene expression (variation in the regulatory sequences). As a proponent of regulation I was floored a few years ago by David Weatherall's challenge that the haemoglobinopathies – the best-understood group of genetic diseases – were entirely a matter of structure. I note with pleasure that David's own followers at Oxford have now discovered that one of these diseases is actually caused by a regulatory 'defect'. The inverted commas refer to the fact that the mutation that causes the anaemia survives in the Melanesian population because it (presumably) protects against malaria.

There are three current topics in genomics that interest me and may become important. The first of these is *haploinsufficiency*, the condition in which a mutation responsible for a largely recessive disease has a significant impact on the health of heterozygous carriers. The condition – 'where half a loaf is not enough' – is not uncommon, especially among genes encoding transcription factors. Civilization (medical care, hygiene and so on) will surely alleviate the impact on carriers. This will allow the frequency of this type of mutant to rise, causing the frequency of the full homozygous disease to rise in turn. The process will take time to have a serious impact, but it is something that we should be aware of and should set about preventing. Obviously common variable immunodeficiency, where only about a tenth of the genetics is understood, is likely to involve this type of effect.

My second topic is *mitigation*. Certain alleles are beneficial but have a deleterious side effect. An example is human leucocyte antigen (HLA)-B27, beneficial for the usual reason among class I HLA genes that it protects against viral infection. This particular allele is known to protect against HIV infection. The side effect is that it increases susceptibility to a range of inflammatory diseases, including acute anterior uveitis and the spondylarthropathies. The gene seems to have undergone mitigation. A proportion of HLA-B27 genes have an unusual sequence motif in their upstream regulatory region that would inactivate their interleukin (IL)-6 response element (although the number of individuals sequenced so far is too small to be certain of this). IL-6 is a cytokine that among other proinflammatory effects upregulates HLA class I gene expression. It seems likely, then, on the basis of this admittedly incomplete evidence, that natural selection retains the HLA-B27 gene in the human population, while at the same time mitigating its proinflammatory effect. This is not simply another example of one gene modifying the effect of another, because the gene is modifying its own function and can therefore be regarded as true mitigation.

My third topic concerns not the behaviour of individual genes but rather the rules of the game. One of the first rules is that genes recombine. The remarkable new discovery is that recombination is highly variable, occurring frequently at *hot spots* scattered throughout the genome and rarely elsewhere. This is of interest to immunology principally because it greatly simplifies the hunt for disease associations, which can now focus on the large blocks of genes that are inherited together, separated by hot spots. But hot spots also interest immunologists for other reasons. As the Jeffreys' group have shown by spermatozoa analysis, they occur at various places in the major histocompatibility complex (MHC) and in various alleles. In at least one instance, an allele that lacks a particular hot spot diverges in evolution, so that the neighbouring exons (and even the promoter) differ quite markedly from other alleles that do have the hot spot. I refer to an old friend familiar to H-2 afficionados, the hot spot

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between exons 2 and 3 of H-2Eb. It is associated with a retrotransposon and is lacking in the highly divergent *p* alleles. Interpretation of this divergence is ambiguous. It could mean that putting neighbouring exons into lock step slows their evolution, or alternatively that it speeds it up.

This is not the only reason for MHC obsessionals like me to wonder about hot spots. For the last 20 years the possibility of recombination within MHC exons has been discussed, in connection with exon diversity and with the transplant resistance mutations. The alternative possibility, of mutation and selection, has also been argued with vigour. Now, at last, spermatozoa recombination analysis seems to open the way for a definitive resolution of the issue. More generally, we can confidently expect molecular analysis to reveal just what factors, genetic and epigenetic, contribute to making a hot spot. The more we learn in that direction, the more we shall understand about the MHC and the other regions of diversification of interest to immunology. Immunologists should keep an eye on four-strand pachytene.

These questions of balance and dysregulation apply in quite another part of the immune system, namely the origins of *autoimmunity*. The present position may be summarized as follows. We know that the anatomical site of dysregulation, among T cells at least, is the cluster around the dendritic cell. It is there that the key decisions in the polarization of the T cell subsets are made, and it is likely that that is where autoimmunity is triggered, either by stochastic imbalance or in the response to infection. The most important recent discovery is that polarization occurs while resting T cells interact strictly within their own cluster (i.e. each dendritic cell is the centre of an autonomous group); upon activation the T cells begin to wander from group to group. The mind boggles at this complexity – the process calls for a systems biology approach.

This little collection could be regarded as no more than wrack at tides end, or the tailings from an old mine. Nevertheless, they make the point that odds and ends may prove worthwhile: not a particularly popular point, perhaps, now that hierarchical teams, structured programmes and institute creep have become the order of the day. Oh dear, yet another grumpy old man.

Vaccine development

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In 10–20 years' time, vaccine development will have advanced a great deal. The brilliantly successful 7–11-valent carbohydrate–protein vaccines against *Streptococcus pneumoniae* will have been supplanted by a much cheaper common protein vaccine consisting of three to five conserved proteins, both outer membrane proteins and those contributing to virulence. These will have been made by recombinant DNA technology. In fact, the search for vaccine candidates by genome mining (or reverse vaccinology) will have been so rewarding that a full meningitis package will also be available (*Neisseria meningitidis* A, B, C, Y, W135; *Haemophilus influenzae B* and non-typeable *Haemophilus*).

The story of diarrhoeal disease vaccines will be slightly less satisfactory, but because of Warren Buffett's fortune having been conjoined to that of Bill and Melinda Gates, the bacillary dysentery vaccine will at last be covering most of the important *Shigella* serotypes. The rotavirus vaccine will have been commodified, with most of the UNICEF tender being filled by manufacturers in India, China, Brazil and Indonesia. Nevertheless, the effective Vi-conjugate typhoid vaccine and the oral mucosal-adjuvanted cholera vaccine will continue to be under-used because they do not fit comfortably into the routine infant immunization programmes.

The three blockbuster anti-cancer vaccines will be in routine use, the third-generation human papilloma virus vaccine now covering 95% of the cancer-causing HPV variants; the hepatitis B having already caused dramatic reductions in carrier rates and beginning to lower liver cancer deaths; the hepatitis C virus limping behind somewhat because of the virus's enormously high mutation rate. At long last, the fourth blockbuster against stomach cancer, *Helicobacter pylori*, will have passed its phase III trials with flying colours and funds to incorporate it into the Global Alliance for Vaccines and Immunization will be sought via the International Finance Facility, Immunization.

The scene for the 'big three' vaccines, HIV/AIDS, tuberculosis and malaria, will still be murky and contentious. Despite the best endeavours of the Global HIV/AIDS Vaccine Enterprise to engender worldwide consensus, the encouraging but not overwhelming clinical trial results of the three front-runners for HIV have left it unclear which should go into the field. In malaria, real progress has come separately from sporozoite, blood stage and liver stage candidates, but arguments continue to rage as to the best adjuvant and how the elements should be combined. Tuberculosis has moved faster than anyone had though possible, the engineered bacille Calmette–Guérin (BCG) with added genes for ESAT-6, Ag85B and Mb72f will be looking really good, but debate will continue about whether the addition of genes for interleukin (IL)-12 and IL-23 represents too great a risk.

Global poliomyelitis eradication having been certified in 2012, the cry for global measles eradication will be in full swing. Proponents point to the last case of indigenous measles in the Americas having been in 2016, but opponents fear the costs for sub-Saharan Africa and India will be too high. The recent success of the inhaled vaccine in 4–6-month-old infants in the face of persisting maternal antibodies will be tilting the vote in favour of the 'yes' camp.

With several new and emerging infections dominating world headlines, it will be good to see that vaccines have emerged from the shadows and now represent the fastest-growing part of the world pharmaceutical market.

Autoimmune escalation: through the crystal ball

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Starting in the very first volume of *Clinical and Experimental Immunology*, my colleagues and I published a series of articles [1–4] on experimental thyroiditis in the rhesus monkey. In 1966 it was already clear that thyroglobulin is a major antigen in human thyroiditis and that it can induce a similar disease in rabbits, guinea pigs, rats and mice by experimental immunization. In addition to antibodies to thyroglobulin, humans with chronic thyroiditis produce a second antibody of distinct specificity reacting with the thyroid follicular cell cytoplasm and, more particularly, with thyroid microsomes (now the antibodies are known to be directed to thyroid peroxidase). At the time we and others were not able to induce the microsomal antibody in subprimate animals but found that it appeared in rhesus monkeys immunized with monkey thyroid crude extract. This finding gave us the unique opportunity to study the relationship between two distinct thyroid-specific antigens, thyroglobulin and thyroid peroxidase. Although we were unable to prepare thyroid microsomes without thyroglobulin as a contaminant, we found we could make monkey thyroglobulin without any trace of microsomal antigen. Immunizing monkeys with purified thyroglobulin induced thyroiditis accompanied initially by antibodies to thyroglobulin. Later, sometimes as long as 100 days later, we found that antibodies to the microsomal antigen (i.e. thyroid peroxidase) arose. We therefore concluded that this antibody was the consequence of the initial thyroid cell damage produced by immunization with thyroglobulin and termed it 'autoimmune escalation'.

It is common to find autoantibodies to multiple organ-specific antigens in the localized autoimmune diseases. In the case of thyroiditis, the presence of antibodies to thyroid peroxidase actually correlates more closely with clinically significant disease than do antibodies to thyroglobulin. We suspect that these are secondary antibodies and indicative of ongoing organ damage. My crystal ball therefore signals to me that broadening of the autoimmune response by the appearance of antibodies to additional organ-specific antigens will provide us with critical information in predicting whether an initial autoimmune response is temporary, self-limited and clinically insignificant or progressive and pathogenic, leading to autoimmune disease.

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Infections, immunopathology and chronic diseases

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Many immunologists' efforts centre around the areas of tolerance and autoimmunity as a means to understand autoimmune diseases. While there is no doubt that true autoreactivity can be induced and may lead to autoimmune disease, details of mechanisms are poorly understood. The recent attempts to invent regulatory T cells, to replace the old ideas of suppressor T cells or idiotypic networks is, in my opinion, just one depressing example of how badly we still do. I should like to predict that a large portion of autoimmune diseases, together with many other diseases that are now called 'essential', 'idiopathic', 'of unknown aetiology' 'degenerative', 'of old age' or 'chronic', may turn out to be the consequences of infection-triggered immunopathologies causing and maintaining inflammatory processes at low levels for long periods of time. This proposal is simple, does not require the invention of yet another regulatory network and can be strengthened by careful, long-term (≥ 20 years) epidemiology using modern sensitive molecular, immunological and socio-medical methods. The one important message the HIV/AIDS epidemic has re-emphasized is that an infection may trigger immunopathological responses that cause overt disease only 10–40 years later, as with leprosy, tuberculosis, syphilis and many parasitic infections.

My crystal ball, then, signals to me changes in our basic understanding of the idea of tolerance, as follows. Operationally, potentially reactive T or B cells against many extralymphatically localized antigens, both self-encoded and infectious, are not usually triggered to cause immunopathological disease before the reproductive period is over (i.e. up to 25 years of age), but may well be responsible for chronic inflammatory processes which, much later in life, become responsible for many life-limiting diseases, including arthritis, arthrosis, hypertensive diseases, atherosclerosis, central nervous system diseases and many others that are currently called idiopathic, degenerative, etc. Accordingly, cytopathic infections (viruses, bacteria, toxins, etc.) kill young hosts. Resistant immunological high-responders have long been selected for survival. Poorly and non-cytopathic infections that we recognize as such may cause various degrees of immunopathological diseases (e.g. hepatitis B, HIV, AIDS). Chronic infections that we do not recognize as such, for whatever reason, may cause disease by chronic inflammation including induction and maintenance of peripheral self-antigen-specific T and B cell responses. Because we do not

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recognize these aetiologies we call such disorders 'autoimmune diseases'. In future we shall call them third-stage consequences of certain infections, as we do today for complications of syphilis, HIV/AIDS, coxsackievirus infections (e.g. dilating cardiomyopathies), salmonella, legionella, toxoplasma and many other infections. The great advantage of this crystal ball view over T_{regs} and other parallel ideas is, of course, that we can do something about these diseases by preventing and/or delaying the slow disease process, through vaccination or antibiotics, anti-viral and anti-parasitic treatment, and by changes in hygiene and public health measures, as has been performed so successfully for acute childhood infections.

Acknowledgements

The Editor is grateful to Amanda McLean-Inglis of Blackwell Publishing and to Daniel Price of the British Society for Immunology for their invaluable assistance in conceiving and preparing this article.