Investigating Ophthalmology with Translational Science
The Weisenfeld Lecture

John V. Forrester

The Mildred Weisenfeld award truly is a magnificent honor to have been bestowed on me. Self-consciously, I can't deny the suitability of the honor, even if the merit in my case can be questioned, and I warm to the task of explaining its aptness. Mildred Weisenfeld, a retinitis pigmentosa sufferer from her teens, is known to the ARVO community for her unstinting and visionary energy in fund-raising, and support for ophthalmic and visual science. This energy was directed not so much with a view to helping relieve the suffering of visually impaired individuals, itself a noble cause, but toward supporting research into the causes of blindness so that new therapies could be discovered to prevent vision loss. She was, indeed, frustrated to realize that in the United States, and almost certainly worldwide, focussed research activity of this nature was scant. It was due partly to her efforts that the National Eye Institute (NEI) now stands where it does, providing support for vision scientists in the United States and beyond, and the ARVO fellowship is indebted to her. Such dedicated Institutions are not available to other nations.

Specifically, Mildred Weisenfeld was addressing the problem of translational science, although this relabeling of an existing but growing activity came into effect only recently. Insightful clinicians for years have understood that developments in science have direct bearing on better ways to treat their patients. Indeed, historically medical scientific discoveries frequently were made by medical doctors, and famous examples abound in all fields of medicine, not least in Ophthalmology. Names, such as Helmholtz, von Graefe, Donders, Bowman, Friedenwald, and Duke-Elder, spring to mind. However, many of these ground-breakers were active during the 19th and early 20th centuries, and in recent years the nonclinical professional basic scientist, whose trade is Big Science, has edged out the patient-oriented Clinician Scientist. This unintended, and possibly self-inflicted exclusion has been felt for nearly 50 years, not only in ophthalmology, but in all fields, as articulated in an editorial from 1983. Evidence that such effects are real is difficult to find, but one measure has been the concern raised in recent years regarding the low numbers of NEI grants awarded to MD versus PhD qualified applicants.

Clinicopathologic and Experimental Studies in Vitreous Hemorrhage

The problem for the nascent clinician scientist is that opportunities for start-up in research may be limited or difficult to identify. I was fortunate when beginning my career as a trainee ophthalmologist to work with a clinician, John Williamson, who understood that the ground for development must be prepared to allow growth. While training with JW, I observed how a shot of intravitreal urokinase restored vision to a patient with diabetes who had been blind for over 5 years due to a nonresolving vitreous hemorrhage. This had a lasting impact on me, and took me to the laboratory to investigate why many dense blood clots in the vitreous failed to resolve.

Several factors conspire to prevent resolution of intravitreal hemorrhage, including a lack of intrinsic fibrinolytic activity of vitreous gel (Fig. 1). However, more importantly, blood clots in the vitreous fail to attract a significant inflammatory response and components of the vitreous appear to modify the behavior of macrophages, in particular inducing the formation of giant cells (Fig. 2). This work required the development of an animal model of vitreous hemorrhage, performed in rabbits under the guidance of WR Lee, ophthalmic pathologist, who demonstrated the great value of morphologic studies for the generation of ideas and new questions. Thus, although this “defective” inflammatory response did not fit the then criteria of a suppressed immune response, as such, it resonated with current concepts of an inadequate “danger” response and presaged the notion of innate immune privilege.

The Effects of Vitreous Components on Cell Behavior

Matrix Components Modify Cell Behavior. The intriguing behavior of macrophages in the vitreous led to further exploration of the cell biology of inflammatory cells and the effect of vitreous constituents, specifically hyaluronan (HA). With EA Balazs, we demonstrated that HA markedly inhibited the phagocytic activity of cultured peritoneal macrophages (Fig. 3). This effect depended on the molecular weight of the hyaluronan, with high molecular weight (HMW) material inhibiting phagocytosis significantly more than low molecular weight (LMW) HA components. This is relevant particularly to the physiology of the vitreous gel, since HA in the adult gel is known to be of HMW with the highest molecular species being present in the cortical vitreous gel, and LMW components occurring in the inner gel layers. In addition, with age the...
vitreous gel degrades in terms of MW and, particularly in inflammation, some very LMW oligosaccharides can be generated. LMW HA oligosaccharides specifically bind receptors on leukocytes, such as CD44, but also can act as “danger” signals binding the pattern recognition receptors (PRR) TLR2 and TLR4 (reviewed by Jiang et al.8). Such moieties actually have a proinflammatory effect mediated through TLRs, but also immunomodulatory effects via CD44 ligation (see below). In contrast, HMW HA species universally dampen inflammatory and immune responses. In retrospect, although our interest lay in impaired inflammatory responses due to vitreous and its content of HMW-HA, our data in fact reveal that LMW HA has a stimulatory effect on phagocytosis (Fig. 3, see effect of oligosaccharide $9.0 \times 10^4$ HA), thus revealing the complex nature of HA immune-inflammatory regulation (for review see the report of Jiang et al.8).

This work was extended to other aspects of inflammatory cell behavior, including neutrophil cell migration (using the Boyden chamber assay) and adhesion to protein-coated and uncoated dishes. The migration studies were performed under the careful tutelage of P Wilkinson using an in vitro model of chemotaxis and the peptide, F-Met-Leu-Phe. Once again, HMW HA was significantly more inhibitory than LMW HA and in this case, although there appeared to be some effect on receptor blockade, the main effect of HA appeared to be mediated by steric hindrance, due to the very large size of the hygroscopic HMW HA molecule.8,9 Further collaborative work with JM Lackie and ASG Curtis also showed a similar MW-dependent effect of HA on neutrophil adhesion.10 On this occasion, the effect of molecular charge on cell behavior was explored since HA is a highly negatively-charged molecule and the possibility of repulsive charge effects between cell surface and substrate, which might explain failure of cell adhesion, were considered. It turned out that charge did not seem to have a significant role. Rather, the viscous nature of the HMW species was the more significant component. However, on the more general question of cell adhesion to charged surfaces, there clearly was an effect since hydroxyl charges appeared to be much more important than other negatively charged groups for cell adhesion.11 HA continues to be of considerable interest to cell biologists. For instance, recent studies have suggested an alternative mechanism for the anti-inflammatory effects of HMW-HA, based on the low binding affinity interactions of HMW-HA with its receptor CD44 and, thus, as multiple HA-CD44 interactions are required for signalling, these accumulate with the size of the HA molecule.12

Overall, these data confirmed the multiple effects of vitreous components on inflammatory cell behavior. Thus, in the presence of a moderate insult, such as an isolated vitreous bleed, intragel blood rapidly clots13 but does not clear quickly due to the poor fibrinolytic activity of the vitreous, while potential scavenging cells, such as neutrophils and macrophages, are prevented from invading the clot in significant numbers by the HMW-HA–rich cortical gel. HA in the vitreous, thus, contributes to the overall tissue-centered innate immune response as a whole.
privilege of the eye (see below), providing a physicochemical barrier to inflammatory cell invasion by blocking cell adhesion and migration; and those cells that do invade are inhibited further in their phagocytic activity. Whether HA modifies the behavior of those macrophages sufficiently to prevent differentiation of alternatively activated macrophages and giant cells is not known. In contrast, in the face of a severe insult, such as that associated with trauma and vitreous hemorrhage, the gel is degraded rapidly, the anti-inflammatory effect is lost, and the blood is cleared. However, the destructive effects of the inflammation on ocular structure lead to consequences, such as traction retinal detachment and proliferative vitreoretinopathy (PVR).14

This, of course, is only part of the story, since there are many other players involved in the eventual damage to the eye in PVR, but the therapeutic, anti-inflammatory effect of HMW HA has been amply demonstrated by its widespread use as a protective viscoelastic agent during ocular surgery.15 This translational component on the use of HA more recently has been extended to the use of HA in stem cell biology and therapy.16

**Cell Migration to Different Cues Is Hierarchical.** One thing leads to another: it was clear from the above data that cell migration itself is regulated by several factors, such as the nature of the substrate on which cells crawl, the firmness of the adhesion of the cell to the substrate and the type of stimulus that induces cell migration. While chemotaxis was accepted by cell biologists as the prototypical cell migration mechanism, other cues were seen to be active, such as haptotaxis (cells moving in response to surfaces of different adhesive) and electrotaxis (galvanotaxis, cells moving directionally in response to an electric field). For instance, we showed that neutrophils could respond to an increasingly adhesive surface generated from different concentrations of immune complexes.17 However, with Colin McClaig and Min Zhao, we demonstrated that electrotaxis is a powerful stimulus for cell migration during many types of cell movement, for instance during inflammation, development, embryogenesis, and wound healing (including the cornea), and that there was a hierarchy of responses to cues with electrotaxis being the strongest cue.18–20

**Endogenous Electric Fields Modify Cell Behavior.** Indeed, the fundamental influence of endogenous electric fields (EF) applies to many physiologic processes. EFs govern the movement not only of single cells, but sheets of cells as well as the coordinated polarization of cells during mitosis (Fig. 4).21 In addition, different cell types migrate either to the anode or cathode, even cells of the same basic type, such as microvascular versus large vessel endothelium.22 This has the effect of controlling such processes as dorsoventral polarization during development and regulating the electric dipole that is present in the eye. In fact, by minimally disrupting EFs, which occur around the lens, it is possible to promote regeneration of the entire mammalian lens after lensectomy (Fig. 5).23

**Translational Science and Preclinical Models**

Much of the above mostly in vitro work investigating basic cellular processes has obvious, but untested relevance for translational science. Preclinical physiologic, pharmacologic, and therapeutic studies rely on experimental models, and my initial interest in ocular inflammation and immune privilege was not diverted irrevocably by our studies in cell biology. Indeed, the issue of why inflammation in the eye was “blunted” has been my main interest since those early days of curiosity as to why blood in the vitreous failed to clear. I, therefore, began to ask questions about inflammation and immune privilege in the eye. To study this, I was fortunate that the model of experimental autoimmune uveoretinitis (EAU) had been developed recently, including the discovery of the major retinal autoantigen, retinal S antigen.24 With reagents from WB Wacker (Proctor Lecturer in 1991), we set up the EAU model in the guinea pig and rat, and with Paul Memenamin, long-time friend and colleague, and now sponsor, we performed some definitive electron microscopy studies.25–27 Later, we used R Caspi’s (Freidenwald lecturer in 2011) model of EAU in the mouse,28 and currently are using the chronic relapsing model in the C57/BL6 mouse.29 This is an excellent model that closely mirrors the disease in humans, and has been the cornerstone of many basic immunologic studies revealing the mixed role of various types of T cells in the pathogenesis of this disease.30–31

**EAU as a Model of Autoimmune Disease.** The model of EAU in the mouse, as for many similar models in autoimmunity, generally is an organ specific disease, in which the antigen is emulsified in complete Freund’s adjuvant (CFA), an oily emulsion containing heat-killed extract of *Mycobacterium tuberculosis* (MTb) strain H37ra, and administered subcutaneously. This has been described by Janeway, as the “immunologists’ dirty little secret,”32 since CFA is essential for the induction of inflammation, and does so by activating the innate immune system via PRRs, which recognize generic molecular patterns on micro-organisms (pathogen-associated molecular patterns, PAMPs). Janeway discovered one group of PRRs, the Toll-like receptors (TLRs), of which there are now between 10 and 13 depending on species.33 In addition there now are many other PAMPs and PRRs, and the entire field of innate immunity has opened.

However, the fact that MTb extract is necessary for induction of EAU is of particular relevance for understanding...
intraocular inflammation (uveitis, uveoretinitis). Clinical uveitis is categorized in two groups: infectious and noninfectious, the latter being considered immune-mediated, if not specifically autoimmune. The distinction between infectious and noninfectious causes, however, is becoming increasingly blurred, and many cases of unsuspected, atypical MTb uveitis are being unearthed. In fact, the burden of tuberculosis (TB) worldwide is enormous with 1.8 billion people being purified protein derivative positive (PPD+ve), indicating previous TB infection and possible continuing latent TB. Only when immunosuppressed as in AIDS patients or even after treatment with “biologics,” such anti-TNFα does extrapulmonary or even residual pulmonary TB manifest itself. The question might be asked: does latent TB act as some form of endogenous adjuvant that is permissive for “immune-mediated disease.” The organ specificity may relate merely to the stochastic random localization of circulating infected monocytes/macrophages, which are the source of the extrapulmonary MTb disease.

**EAU as a Pre-Clinical Model for Control of Sight Threatening Intraocular Inflammation.** EAU has a long and respected history as a preclinical model for studies of sight-threatening intraocular inflammation (IOI). Current management of IOI is a paradigmatic example of how translational science impacts on medical therapies. Before the era of steroids, patients with IOI/uveitis universally had a poor visual prognosis, in part from the direct retinal damage, but also from the ocular side effects of inflammation, including cataract and glaucoma. However, once steroid therapy became the standard of care, it was quickly realized that the drug had many side effects and prolonged use of steroids for the treatment for IOI was not an option. Therefore, many patients were given only short-term courses of treatment which resulted in recurrence of disease and loss of vision.

In 1981, RB Nussenblatt, joint Proctor lecturer with WB Wacker in 1991, reported on the effectiveness of cyclosporine in controlling inflammation in EAU in the rat. This was the first preclinical study in IOI and led to the introduction of non-steroidal immunosuppressants for the treatment of sight-threatening IOI in patients. Since then, several other immunosuppressants have been introduced, all of which have been tested in preclinical studies of EAU. The standard therapy of severe uveitis (IOI) in many countries now is combination therapy with low dose steroid plus one or more immunosuppressant, such as cyclosporine, mycophenolate mofetil, azathioprine, or tacrolimus, tapering the therapy as the inflammation is controlled. The prognosis for IOI patients has been transformed by this translational research and most patients do not need to lose vision. The main confounding factor now is whether the health care systems in most countries can afford to provide the therapy.
In reaching the current clinical standard of care, EAU has served as an excellent model for the study of many other potential therapies. These include pharmacologic agents, peptides, and gene therapies, monoclonal antibodies (biologics) and T cell–directed therapies (Table 1). Almost all of these have shown some inhibitory effect but for a variety of reasons, including side effects and toxicity, few have reached the clinic. Several agents still are under consideration (Table 2) and the EAU model remains the centerpiece for preclinical testing in this area.

Despite these advances, a proportion of patients remain refractory or intolerant of combination therapy with steroids and immunosuppressants, and further novel treatments have been sought. The first anticytotoxic therapy in I01 was reported by Andrew Dick, also my good friend and colleague and cosponsor for this presentation, using an anti-TNFα fusion protein, once more using the EAU model. This had the remarkable effect of preventing retinal tissue damage while having minimal effect on cellular infiltration.40 This observation has not only led to the increasing use of anti-TNFα therapies for control of IOI but also the observation led to the realization that some of the nondamaging macrophages might suppress disease (myeloid derived suppressor cells, MDSCs),41 which since have been tested directly in the EAU model.42 Further work in this area of novel therapy for IOI is continuing.

### Cell Based Therapies for Control of Intraocular Inflammation

EAU as a model lends itself as a test bed for novel therapies for autoimmune disease. Because of its clear end points and defined clinical grading system, it has been trialed in a variety of novel therapies, including gene therapies and cell-based therapies, such as MDSCs and mesenchymal stem cell therapy (MSCs).43 Most experience in this field has been in the use of tolerogenic dendritic cell (tolDC) therapy, in which autologous bone marrow–derived dendritic cells are inoculated subcutaneously or intravenously to prevent EAU. Dendritic cells (DC) were discovered by RM Steinman, for which he was awarded the 2011 Nobel Prize, and which he showed to be the antigen-presenting cell that activates naïve T cells, that is they are the initiators of adaptive immunity to foreign antigens (reviewed by Banchereau and Steinman44). Later, he showed elegantly that, in the resting, unchallenged state, DC are the main regulators of the immune response by promoting tolerance to self antigen. DC underpin the several tolerance mechanisms that exist to control autoimmunity, including immune privilege in the eye (reviewed previously45,46). This they do, in part, by inducing a subset of T cells, namely T regulatory cells (Tregs), which have been identified as essential for maintaining tolerance and prevention of autoimmune disease.

Autologous DC therapy is highly flexible, that is it can promote immunity, for example against tumour or infection, such as HIV, or tolerance as in preventing allograft rejection or treating autoimmune disease (Fig. 6). DC in mice are isolated from tissues, such as spleen and bone marrow, and in humans can be separated as precursor cells from blood. With appropriate conditioning of the cells in vitro, they can be polarized toward immunogenicity or tolerogenicity. Clinical trials of immunogenic DC have been initiated in cancer therapy,47 but tolerogenic DC have not yet progressed beyond the preclinical stage, including uveitis. However, they have been shown to inhibit EAU in the mouse, which is promising.48,49

Since tolDC act by inducing Tregs, and Tregs occur naturally in the blood or can be induced by culture in vitro with IL-2 and antigen, it has been proposed that Tregs can be used directly to control autoimmune disease rather than first inducing them in vivo with tolDC. However, this also has not progressed yet to clinical use.50

Cell-based therapy faces many challenges, a general one being meeting the requirements of Good Manufacturing Practice (GMP). Each of the specific therapies also have

### Table 1. Previous Preclinical Studies in EAU

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>Gene therapy</th>
<th>Peptides and gene therapy</th>
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<tbody>
<tr>
<td>Anti-retinal antigen</td>
<td>Cytokines (e.g., INF-2)</td>
<td>VIP</td>
</tr>
<tr>
<td>Anti CD4</td>
<td>Calcium</td>
<td>IL-1 receptor antagonist</td>
</tr>
<tr>
<td>IL-2R inhibitor</td>
<td>Intracellular</td>
<td>T2MSH analogues</td>
</tr>
<tr>
<td>Anti-ICAM-1 and LFA-1</td>
<td>Angiostatin</td>
<td>Gene therapy (e.g., anti-IL 10, CTLA4+Ig)</td>
</tr>
<tr>
<td>Anti-CCR5</td>
<td>Angiotensin II type 1 receptor blocker</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>Anti-α4 integrin</td>
<td>Angiotensin II</td>
<td>Anti-retinal antigen</td>
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<tr>
<td>Anti-IL2R</td>
<td>Angiotensin IV</td>
<td>Anti CD4</td>
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<tr>
<td>Anti-IL12</td>
<td>Angiotensin V</td>
<td>Anti CD4</td>
</tr>
<tr>
<td>Anti-IL17A</td>
<td>Angiotensin VI</td>
<td>Anti CD4</td>
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<tr>
<td>anti-MIF</td>
<td>Angiostatin</td>
<td>Anti-retinal antigen</td>
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<tr>
<td>anti CD 157</td>
<td>Angiotensin II</td>
<td>Anti-retinal antigen</td>
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<tr>
<td>T-cell–directed therapies</td>
<td>Angiotensin II</td>
<td>Anti-retinal antigen</td>
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<tr>
<td>T-cell vaccination</td>
<td>Angiotensin II</td>
<td>Anti-retinal antigen</td>
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<tr>
<td>TCR inhibitors</td>
<td>Angiotensin II</td>
<td>Anti-retinal antigen</td>
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In reaching the current clinical standard of care, EAU has served as an excellent model for the study of many other potential therapies. These include pharmacologic agents, peptides, and gene therapies, monoclonal antibodies (biologics) and T cell–directed therapies (Table 1). Almost all of these have shown some inhibitory effect but for a variety of reasons, including side effects and toxicity, few have reached the clinic. Several agents still are under consideration (Table 2) and the EAU model remains the centerpiece for preclinical testing in this area.

### Table 2. Some Current Preclinical Studies in EAU

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic agents/drugs</td>
<td>FTC 20</td>
</tr>
<tr>
<td>Agonist peptides</td>
<td>SOCS1 signalling agonist?</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>Complement inhibitors</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Oral tolerance therapy</td>
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<tr>
<td>Monoclonal antibodies</td>
<td>Anti-IL-2t Daclizumab</td>
</tr>
<tr>
<td>Small molecule inhibitor</td>
<td>Anti-IL-6</td>
</tr>
<tr>
<td>Gene therapy</td>
<td>Cytokines (e.g., INF-2)</td>
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Cannabinoids are discovered by RM Steinman, for which he was awarded the 2011 Nobel Prize, and which he showed to be the antigen-presenting cell that activates naïve T cells, that is they are the initiators of adaptive immunity to foreign antigens (reviewed by Banchereau and Steinman). Later, he showed elegantly that, in the resting, unchallenged state, DC are the main regulators of the immune response by promoting tolerance to self antigen. DC underpin the several tolerance mechanisms that exist to control autoimmunity, including immune privilege in the eye (reviewed previously). This they do, in part, by inducing a subset of T cells, namely T regulatory cells (Tregs), which have been identified as essential for maintaining tolerance and prevention of autoimmune disease.

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Cell-based therapy faces many challenges, a general one being meeting the requirements of Good Manufacturing Practice (GMP). Each of the specific therapies also have
particular challenges. For instance, MSCs and MDSCs face the difficulty of phenotype characterization, since there are few markers for these cells. However, in Phase I clinical safety trials they have been shown so far to have minimal side effects. ToTDC face the problem of stability, antigen specificity and optimal tolerizing procedures, which theoretically include gene modification. Treg therapy faces similar problems, including antigen specificity, but more importantly whether sufficient numbers of Tregs can be generated in vitro or purified as freshly isolated cells to be sufficiently active in vivo after adoptive transfer.50,51

Despite these caveats, cell-based therapy is an attractive option for the new era of personalized medicine since it involves the use of autologous cells (or same donor cells in treatment of graft-versus-host disease, GvHD) and has the potential to avoid all the continued side effects of current immunosuppressant therapies.

**ROLE OF THE CLINICIAN SCIENTIST**

**The Clinician Scientist as a Leader**

The need for clinician scientists in bringing advances in the laboratory to the clinic is self-evident. What is not so clear is his/her role. In my view, the role is as leader of the combined medical and scientific team: this requires full knowledge, if not actual hands-on preclinical experience, of the therapies to be tested and how they are likely to perform in man. A deep understanding of the science behind the drug, therapy, intervention, or procedure is mandatory in this role.

This experience can be gained by undergoing preclinical training using animal models, developing molecular and cell biologic skills in the laboratory, observing the outcomes first hand in the in vivo preclinical models as well as other potential activities, such as preparing the material for use in man. This laboratory/preclinical experience obviously is to be combined with clinical training in the discipline and subspecialty training in the area of interest. Innovative schemes supporting such developments already have been set up in some countries.52

**The Clinician Scientist Is Responsible for Ensuring Good Clinical Outcome Measures**

A primary function of the clinician scientist is to design, manage, and analyze data from clinical trials. In addition, (s)he has responsibility for ensuring that ethical/regulatory body approvals are secured. This in itself demands considerable knowledge and training. Importantly, it requires that the clinician scientist can reassure his laboratory colleagues that the clinical outcome measures that (s)he is going to use to test the new therapy are robust. Ophthalmology has some advantages over other disciplines in that there are objective quantifiable outcome measures, such as tests of visual function and the many imaging modalities available, particularly optical coherence tomography (OCT). However, some conditions, such as uveitis, present considerable clinical heterogeneity and complexity, and only now are coming under some level of standardization in terms not only of their degree of severity, but even their phenotypical description. The recent international multicenter initiative in this context is greatly to be welcomed.53,54

**Training/Mentoring the Clinician Scientist**

Clinician scientists historically have emerged almost by accident, driven mainly by the curiosity and energy of the individual. In today's medical environment, with the developments of Big Science, a formal training program probably is optimal for producing a cadre of such individuals. Several such programs have been developed in the United States and Europe, and other countries worldwide. However, not all have been successful, and in part this is due to the assumption that simply by setting up such program, individual trained experts will surface.

In fact, there are many obstacles to generating the clinician scientist who also is to be a future leader. First, it is not clear...
how many are required on a national level and how they will integrate with the strategy of a national health care plan for service provision, or even for planned research and innovation. In one sense this depends on the “unmet medical need,” which itself has not been quantified to any great extent. Second, the type of individual to be recruited to a clinical scientist training program should have many qualities—intellectual, practical, and empathetic—over and above the already expected high standard of recruits to higher education in Medicine and Science. Third, the recruited individuals must realize that the chances of them achieving a successful outcome to their career plans are not high (“many are called but few are chosen”) and when they take up the baton, they are embarking on a risky venture.

However, it is important to encourage future potential trainees, as well as to mentor and monitor the trainee. Although Big Science can be daunting, for the type of individual described above, the intellectual and work-load aspects are fully within their grasp. Importantly, at the present time, our current clinician scientist leaders have a duty to engage in this activity of encouragement, promotion and mentorship of trainee clinician scientists,55 to nurture and guide them in their aspirations, and to break down the language barrier that exists between pure scientists and clinicians,56 so that we can prepare fertile ground for these individuals to thrive. Most importantly, the ultimate purpose of mentorship of trainee clinician scientists,55 to nurture and guide them in their aspirations, and to break down the language barrier that exists between pure scientists and clinicians,56 so that we can prepare fertile ground for these individuals to thrive. Most importantly, the ultimate purpose of keeping the patient and his good health as the centerpiece of this endeavor, will be met if these considerations are a common goal.

**Acknowledgments**

I am indebted to my several mentors mentioned above, and to my colleagues and collaborators in the many publications that I have been privileged to share with them, and especially to my promoters for this award, Paul McMenamin and Andrew Dick.

**References**


