Editorial ....................................................................... 3
Health scares—a very English pastime? ........... 3
Dendritic Cells are Key Regulators of Intestinal Immune Responses .......................... 5
Commentary—How Inflammation Overcomes Suppression .................................. 10
Dendritic Cells, Mucosal Immunity and Peripheral Tolerance ................................ 11
Mucosal Immunology Affinity Group Workshop–Harrogate 1998 ................ 15
The First European Mucosal Immunology Meeting ...................................... 17
Charles Elson, M.D., President of the Society for Mucosal Immunology .... 18
Announcements ..................................................... 19
Editorial

In the first issue of Mucosal Immunology Update in 1998 (Vol. 6 #1), there was a cry from the heart of the editorial committee to the effect that we wished MIU to become much more participatory, and to include submissions of any kind from the membership. One year on, the membership have made their views clear–there have been no unsolicited articles. This outcome, although not unexpected, is extremely disappointing. I was always under the impression that immunologists would do pretty much anything to get their name in print, so either this premise is false, or perhaps the membership feels that an article in MIU is on par with one in the Mongolian Journal of Proctology.

Unfortunately, therefore this issue follows the usual format, with some modifications. I have commissioned two mini-reviews from Jo Viney and Gordon MacPherson on dendritic cells. I have also included two meeting reports. The first is the successful first European Mucosal Immunology Meeting at St. Bartholomews Hospital and the second is the mucosal immunology symposium held as part of the British Society for Immunology’s annual meeting in Harrogate just before Christmas. There is also a commentary from Yoshi Ohtsuka on a seminal paper which appeared in Nature recently showing how interferon-γ interrupted TGFβ signalling, of great relevance to mucosal immunology. Finally, there is a personal, more philosophical piece, on the damage done to UK mucosal immunology, IBD research and public health by repeated scare stories in the media (fuelled by clinical investigators) about Crohn’s disease.

Tom MacDonald
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Health scares— a very English pastime?

Tom MacDonald
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I had the pleasure of attending the recent meeting on coeliac disease in Naples and was very impressed by the detailed analysis of the way that transglutaminase can modify gliadin peptides to make them stronger T cell immunogens. High quality science, good food, convivial hosts and a beautiful location made it a very pleasant few days. Arriving back in England, checking my e-mail at home, I found a message from Ian Sanderson to let me know about a recent story in the British media. If you don’t care about the UK then stop reading now because otherwise this piece will seem too parochial.

While I was in Naples, there had been a national TV news item, with an interview, and questions to government health ministers, about the possibility that Crohn’s disease is caused by Mycobacterium paratuberculosis in the drinking water in household taps (a few years ago it was in milk). Thinking perhaps that there was a blockbuster paper about to come out on this topic, I went directly to the scientific source of these allegations. There was no paper, i.e., no data. It was merely a rehashing of an old story. The source of the allegation felt duty bound, after much pressure and soul searching, to go to the media with his fears! I was overwhelmed by their sense of duty.

A terrible sense of déjà vu came over me–here we go again! We have just been through this in the UK where the publications and public pronouncements of some individuals on measles and Crohn’s disease led to a major public health scare and a drop in the number of infants receiving MMR vaccine. The same group also implied in the media, but not in the scientific press, that MMR might cause autism. This was not buried in some late night regional bulletin, but on the main evening news from the BBC. At significant cost, the MRC and Department of Health, understandably worried about the drop in vaccination, are trying to allay the fears of the public over this issue.

For some reason, health scares happen frequently in the UK, although obviously when it deals with Crohn’s it has a particular resonance for GI immunologists. In recent years there have been fears about salmonella in eggs, listeria in soft cheeses, and most famously, BSE in cattle. The very latest is fears over the safety of genetically modified foods–so called Frankenstein foods. In all cases the media have
given these issues a very high profile and in a highly sensationalist way. It is very easy for scientists to blame the media for this and say they distort the facts. However this is fallacious; journalists may use words that scientists do not like, but they are only flushing out a story with an alleged scientific basis. Don’t shoot the messenger.

There is however a broader issue, is it something peculiar about the United Kingdom that allows this sort of thing to happen? From my own knowledge, these ideas do not seem to be taken seriously elsewhere. Is it the UK tradition of tolerance of eccentricity that allows this kind of thing? I am not so sure of this because the UK-based researchers who have come up with most of these ideas frequently are invited to international meetings. Is it in the interest of completeness, paranoia or as light relief that this occurs?

Crohn’s health scares are quite recent but the search for the etiologic agent has a chequered history. I therefore decided to take a trawl through the literature on etiologic agents in Crohn’s disease over the last 30 years, excluding the more fanciful ones such as cornflakes and toothpaste. The results of my efforts are shown in the table. I have only shown the main papers, in many cases the same groups have published a series of papers around the same putative etiologic agent. Of the 27 papers shown (there is not enough space to include the extensive number of papers debunking most of this work), 11 were in the Lancet, seven were in Gastroenterology and the work is dominated by UK investigators. Why the Lancet, a London-based publication, and not the New England Journal of Medicine? Is this again a reflection of something peculiar about the UK? The Lancet is a high profile journal and it must surely realize that its publications can have major implications for public health. Who referees these papers? I have never met anyone who admits to this, although many of my colleagues are very happy to announce that they have refereed other papers which appear in prestige journals.

I have always also detected a sense of zealotry in those who propound these new ideas. They are the visionaries, helping humanity to prevent a devastating disease such as Crohn’s. The rest of us are luddites, gnawing away at minor issues while they deal with the big picture. The usual historical examples of people who had major ideas which were rejected by their peers at the time is trotted out, with the unspoken implication that they are amongst these luminaries. What is forgotten is that for every correct idea before its time there are tens of thousands which are wrong.

What particularly saddens me is that whenever a new idea comes out, such as measles and Crohn’s, a number of other investigators try to repeat the work. The fact that no measles genetic material can be detected in Crohn’s disease by PCR although it is alleged to be detectable by immunostaining is enough to set the alarm bells ringing. After the initial publication, there is usually an unseemly debate in the letters section of the Lancet, and as the negative papers start to appear in other journals, more correspondence about why the original observation could not be repeated. The idea then fades like the cheshire cat. Overall however, my major thought is of the sheer waste of time and effort in trying to confirm the poor science invariably associated with these “breakthroughs”. Personally I refuse to become involved in any of this because I have enough problems doing my own research without trying to confirm someone else’s half-baked ideas.

Whenever I get into a debate about the cause of Crohn’s disease and recite the usual notions about the normal flora and disordered T cell responses in the gut wall, I try to base my argument largely on the data that in this area at least, different people in different places in the world get the same results. The mouse models are also very strong evidence. There is reproducibility of observations which then form a firm basis for further studies. Looking at the table it is also clear that the idea that the normal flora might be important is quite old. But there is always a whisper—remember Helicobacter pylori. Is it the fear of being the person who rejected the paper to discover the cause of Crohn’s disease which explains the suspension of critical faculties in this area? This should not matter, if it is true, the paper will get published somewhere, and anyway referees are usually anonymous. I have always considered the H. pylori argument to be overstated. The failure to recognize H. pylori in the stomach says more about the development of upper GI endoscopy and gastroenterologists than anything else.
There is also a very real down-side to all of this. There is very little work funded by the major charities or government on inflammatory bowel disease immunology in the UK. The British Digestive Foundation supports some, but it is very minor league. Do the individuals who announce these health scares and “breakthroughs” do it out of frustration at lack of funding and are they trying somehow to bypass peer-review to some extent? Personally I think that it exacerbates rather than remedies the problem. It cannot be good for IBD research in the UK for the chief medical officer of health of England to write to every doctor in the country saying that the fears over MMR and Crohn’s are unfounded. I remember a few years ago, when I had a grant funded by the Wellcome Trust, that I had to take out all of the work using patient material and concentrate on mechanisms in model systems. There is a perception in the UK that gastroenterologists are not very academic (with apologies to those who are) and that the drug companies keep them well supported. As I write this article, large numbers of UK-based gastroenterologists are being flown to Orlando for the AGA by pharmaceutical companies. The perception that GI research is somewhat inferior extends to others working on mucosal inflammation, we are all tarred with the same brush. Some aspects of mucosal immunology are well supported, such as mucosal vaccination where there are a number of very eminent groups. It is therefore not any particular bias against GI research, but specifically IBD immunology research.

This is a very bad situation because IBD is quite common in the UK and leads to substantial morbidity and economic cost to the country. Any new treatments which might help the patients have to be based on understanding the disease mechanisms. Anti-TNF antibody is a very good example and will undoubtedly help a lot of patients. My only problem is that I cannot help but feeling that when I revisit this area ten years hence, I will have a few more papers to add and there will be a lot more health scares. Then again, I could be wrong, perhaps, a cause of Crohn’s will be found, but I wouldn’t bet on it. Complex problems rarely have simple solutions.

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**Dendritic Cells are Key Regulators of Intestinal Immune Responses**

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The intestinal immune system has developed extremely elegant methods of immunoregulation. Healthy individuals are capable of mounting effective immune responses to the many pathogens which may be encountered via the oral route, while avoiding harmful inflammatory responses to innocuous luminal antigens (Ag). Since we are tolerant to the soluble dietary Ag we ingest with every meal, the classical view of immunoregulation in the
gut is that soluble protein Ag elicit tolerance, whereas particulate Ag generate active protective immunity. In reality, this is rather an over-simplification since most of the population are tolerant to their own commensal bacterial flora, which are clearly non-soluble, non-dietary Ag. The fact that we can mount vigorous responses to foreign microorganisms and even the commensal bacterial flora of others, while remaining tolerant to our own commensal flora, serves to highlight the extent to which intestinal immune responses are regulated. It is clear that these regulatory processes are paramount to healthy living. Common consequences of tolerance breakdown are food allergies and inflammatory bowel disease (IBD), both of which can cause morbidity and, in severe cases, mortality.

Overall, the field of intestinal immunoregulation is a fascinating area giving rise to many pertinent questions. How does the intestinal immune system carry out this important homeostatic function and at what level is it regulated? What are the relative roles of the different antigen presenting cells (APC) in the gut and is it possible that the same APC can function to promote both consequences of antigen feeding—tolerance and immunity. These are just a few of the many types of questions that still need to be addressed in mucosal immunology. In this review, we will summarize some of the current views and hypotheses that abound today.

**Antigen presenting cells in the intestine**

The organized and diffuse compartments of the gut-associated lymphoid tissues (GALT) contain a variety of different types of professional APC, including dendritic cells (DC), B cells and macrophages, as well as less conventional APC, such as intestinal epithelial cells (IEC). The Peyer’s patches (PP) are classically considered to be the major site for immune induction in the intestine and it is generally assumed that many luminal Ag gain access to the GALT via M cells in the PP epithelium. PP contain many DC-like cells, which are particularly prevalent beneath the dome area of the PP, as well as in the interfollicular T cell zones of the PP, in addition to B cells and macrophages. However, since the surface area of the PP is small in comparison to that of the villous epithelium, it is probable that other alternative routes are important for Ag entry and subsequent presentation. Soluble Ag in particular may enter the gut through conventional enterocytes by transcytosis or endocytosis. Ag entering via these routes is likely to come into contact primarily with lamina propria (LP) APC. In the LP, there is an extensive network of MHC Class II+ cells with the morphology of DC. MHC Class II+ cells with DC-like morphology have also been detected residing between IEC, although whether these cells are DC remains unclear and their function has not been studied in detail. It should also be noted that MHC Class II+ IEC can themselves present Ag to T cells, although whether and how epithelial cells can act as APC for MHC class II-restricted CD4+ T cells remains controversial. For the purposes of this overview, we will focus on the phenotype and function of the intestinal immune system.
of DC in the gut and their role in tolerogenic and immunogenic Ag presentation (Fig. 1).

**Mucosal DC**

In the small intestine, various DC populations have been described in both the PP and LP. In the PP, two distinct populations can be distinguished using the DC-reactive monoclonal antibodies N418, NLDC-145, M342 and 2A1. The first DC population appears to be relatively undifferentiated, is negative for NLDC-145 and M342 and is found in the subepithelial dome region of the PP and throughout the follicle, sparing the germinal centre. The second, an interdigitating population, appears to be more mature and is found in the interfollicular T cell regions of the PP and reacts with antibodies to all four DC-specific markers. Functional studies reveal that PP DC can prime T cells after pulsing with Ag in vitro or after oral administration of Ag in vivo. However, it should be noted that the DC described in those studies may well have become activated during culture in vitro, thereby altering their intrinsic functional properties.

Although DC have also been described in the LP, their paucity has hindered detailed analysis of their phenotype. In order to learn more about the nature of DC in the gut and in the LP in particular, we have recently utilized Flt3 ligand (Flt3L), a growth factor that dramatically expands DC in vivo. Utilization of Flt3L to expand DC has permitted us to phenotypically and functionally analyze intestinal DC in their natural, unmanipulated environment.

**Effects of Flt3L on intestinal DC**

Mice treated with Flt3L for 10 consecutive days show a dramatic increase in the levels of CD11c+ve MHC class II+ DC in both the organized and diffuse lymphoid tissues. In the LP, increased DC numbers are visible in both the villous and crypt regions. In the PP, the distinct populations of DC localized to the dome and interfollicular regions are equally expanded, with no apparent preferential increase in either subpopulation. From our studies, it appears that Flt3L simply expands mucosal DC, resulting in more abundant DC populations which maintain exactly the same phenotype as are present in the normal intestine. It is also clear that Flt3L does not induce DC activation. Multi-color flow cytometrical studies have demonstrated that the majority of freshly isolated cells from GALT of Flt3L-treated mice express high levels of MHC Class II and low levels of the costimulatory molecules CD80 and CD86—a phenotype consistent with mature, resting DC. Despite their resting phenotype, these cells are fully functional, as evidenced by their ability to process and present Ag in in vitro Ag loading assays (Viney, unpublished observations). In further support of the functionality of Flt3L-expanded DC, we have observed that these cells are fully responsive to inflammatory signals in vitro and in vivo. Such inflammatory stimuli promote DC activation and give rise to the associated increase in costimulatory molecules.

**Mucosal DC are intrinsically tolerogenic APC in vivo**

As we have discussed, there are many indications that DC are constitutively present throughout the GALT, yet the default response to orally administered Ag is tolerance, not activation. This may indicate one of several possible scenarios: i) that intestinal DC are non-functional in normal, healthy individuals ii) that alternative intestinal APC types are preferentially involved in tolerance induction or iii) that intestinal DC can function in a tolerogenic manner. In order to test these hypotheses and examine whether the increased numbers of DC would influence tolerance induction, we treated mice with Flt3L to expand intestinal DC prior to feeding soluble ovalbumin (OVA). We found that mice treated with Flt3L prior to OVA feeding exhibit more profound tolerance than that seen in equivalent OVA fed control mice. The increased tolerance in Flt3L-treated animals is evident in terms of both DTH and Ag-specific proliferative responses. In addition, Flt3L-treated mice show greater inhibition of OVA-specific serum IgG1 and IgG2a Ab titres after OVA feeding than equivalent PBS controls. In all cases, the enhanced tolerance exhibited by Flt3L-treated mice is most dramatic in mice fed low doses of Ag which are generally ineffective in control animals.

These results indicate that DC may play a pivotal role in tolerogenic antigen presentation in the intestine. The fact that there does not appear to be a preferential increase in any individual DC subset after Flt3L-treatment, or any deviation from the normal DC tissue localization, suggests that the enhanced tolerance observed in Flt3L-treated mice is most likely attributable to the increased probability of a naive Ag-specific T cell coming into contact with...
a tolerogenic DC in the intestine (Fig. 2). Our findings are, however, in direct contrast to previous reports that intestinal DC isolated from Ag-fed mice are immunostimulatory in vitro. We believe that these apparently disparate results may simply reflect the difference between analyzing DC function in situ using Flt3L and analyzing isolated DC in vitro, since the procedure of removing DC from their local tissue microenvironment is known to promote DC activation.

We decided to test whether intestinal DC expanded by Flt3L are intrinsically tolerogenic, or whether they can support active immune responses by examining responsiveness in Flt3L-treated mice following immunization with the potent mucosal immunogen and adjuvant cholera toxin (CT). We found that Flt3L-expanded DC can not only support, but actually enhance the protective response to CT. Compared with PBS-treated controls, Flt3L-treated mice that have been orally immunized with a sub-optimal dose of CT show dramatically increased CT-specific protection against subsequent intestinal challenge. Most strikingly, Flt3L-treated animals exhibit significant anti-CT protective responses when immunized with very low doses of CT which are essentially ineffective in PBS-treated controls. Furthermore, the increased resistance to CT-challenge afforded by Flt3L treatment is accompanied by enhanced local and systemic CT-specific IgA Ab levels.

How can intestinal DC be both tolerogenic and immunogenic APC?

The results described above clearly indicate that both immunogenic and tolerogenic intestinal responses can be heightened in the presence of increased numbers of intestinal DC, but how is this achieved? Recently, it has become apparent that the levels of the costimulatory molecules CD80 and CD86 on the APC surface can critically determine whether the outcome of an antigenic encounter leads to tolerance or active immunity. APC which express low levels of CD80/86 appear to promote T cell tolerance by preferentially signalling through the high affinity CTLA-4 receptor on T cells, while APC expressing high levels of CD80/86 deliver positive, stimulatory signals to the T cell via the CD28 receptor on T cells. We have evidence to suggest that CT can enhance CD80/86 expression on Flt3L-expanded intestinal DC, thereby inducing their activation. Thus, we believe that the augmented anti-
CT protection observed in Flt3L-treated mice immunized perorally with CT can most likely be attributed to the increased number of DC now capable of providing an efficient costimulatory signal to intestinal T cells through the CD28 receptor. In further support of this hypothesis, we have found that activating Flt3L-expanded DC with the proinflammatory cytokine, IL-1α at the time of feeding soluble OVA mimics the adjuvant effects of CT in vivo. As such, treating mice with Flt3L in combination with IL-1α overcomes the default tolerogenic response normally associated with Ag feeding and instead promotes a powerful immunogenic response.

**Summary**

These studies suggest that DC may be well-positioned to regulate the qualitative nature of intestinal immune responsiveness and provide us with an interesting working model (Fig. 1). As such, intestinal DC which encounter Ag in the absence of an inflammatory signal elicit the default response to an orally administered Ag i.e. profound systemic tolerance. Naturally, in the presence of greatly expanded DC numbers, such as after Flt3L-treatment, the level of tolerance induced by Ag feeding is dramatically enhanced (Fig. 2). In contrast, if intestinal DC encounter Ag together with an appropriate inflammatory signal, such as that delivered by CT, or IL-1α, the DC become activated to express high levels of the costimulatory molecules CD80/86 and the outcome of the response is active immunity (Fig. 1). Again, this response is exaggerated in the presence of increased DC numbers, leading to increased responsiveness (Fig. 2).

This model has important implications in terms of mucosal adjuvant design. Clearly, a major obstacle in the design of mucosal vaccines is that most soluble Ag encountered via the oral route promote tolerance, unless administered with an appropriate adjuvant. Although CT is widely recognized as a powerful immunogen and adjuvant that can prevent tolerization to coadministered soluble proteins in rodents, it is not well tolerated in humans. Mutant CT molecules have been generated that retain adjuvant activity without the associated toxicity. Nevertheless, these molecules are immunogenic when administered to research animals. This may prevent their repeated use as mucosal adjuvants, since pre-existing immunity to CT reduces its effectiveness as an adjuvant. There is therefore a need to develop alternative, safe and effective mucosal adjuvants. Our studies suggest that Flt3L, used in conjunction with an inflammatory mediator, such as IL-1α, may be a reagent useful in the design of mucosal immunization strategies.

**Acknowledgments**

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**References**

Commentary

How Inflammation Overcomes Suppression

Inhibition of transforming growth factor-β/SMAD signalling by the interferon-γ/STAT pathway.

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Transforming growth factor-β (TGF-β) and interferon-γ (IFN-γ) have opposite effects on diverse cellular functions, but the basis for this antagonism is not known. TGF-β signals through a receptor serine kinase that phosphorylates and activates the transcription factors Smads 2 and 3, whereas the IFN-γ receptor and its associated protein tyrosine kinase Jak1 mediate phosphorylation and activation of the transcription factor Stat1. Here we present a basis for the integration of TGF-β and IFN-γ signals. IFN-γ inhibits the TGF-β-induced phosphorylation of Smad3 and its attendant events, namely, the association of Smad3 with Smad4, the accumulation of Smad3 in the nucleus, and the activation of TGF-β-responsive genes. Acting through Jak1 and Stat1, IFN-γ induces the expression of Smad7, an antagonistic SMAD, which prevents the interaction of Smad3 with the TGF-β receptor. The results indicate a mechanism of transmodulation between the STAT and SMAD signal-transduction pathways.

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Comment

Transforming growth factor (TGF-β) is an important cytokine at mucosal surfaces and throughout the body. TGF-β knock out mice develop chronic inflammation in many tissues, including the gastrointestinal tract. TGF-β is produced by several cell types in the intestinal mucosa including epithelial cells and macrophages. Its expression is particularly increased in inflamed mucosa of patients with ulcerative colitis (UC) and Crohn’s disease (CD), localized mostly to inflammatory cells of the lamina propria. It is considered that TGF-β is also very important in modulating epithelial cell restitution. TGF-β is also known as an antigen-non-specific suppressor cytokine, released from the regulatory T cells that mediate active suppression against orally administered antigen. In studies of multiple sclerosis (MS) patients, short term cultures of blood lymphocytes resulted in an increase in the frequency of MPB specific T cells that secreted TGF-β1 (Th 3 cells) in the MBP-fed patients compared with that of the non MBP-fed patients. There are a large number of mouse models of IBD. Most of these models show a large increase in cells with a Th1 type cytokine pattern. Transfusing CD4+CD45RBhi T cells into SCID mice causes colitis, which can be prevented by the simultaneous infusion of CD4+CD45RBlo cells. The protective effect of the RBlo cells is inhibited by anti-TGF-β, but not anti-IL-4. Mucosal administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS) also induces IBD like colitis, with infiltration of Th1 type T cells. However, feeding haptenated protein abrogates this Th1 responsiveness and increases production of TGF-β by PP and lamina propria T cells. Disease is exacerbated in tolerant mice by treatment with anti-TGF-β antibody. These studies indicate that inflammatory responses in the gut can be regulated through the balance between IFN-γ/Th1 cell responses and TGF-β/Th3 cell responses.

In this article, Ulloa et al have worked out how IFN-γ can overcome the immunosuppressive effect of TGF-β. It was, first, shown that IFN-γ inhibits the TGF-β signal-transduction pathway in U4A/Jak1 cells which expressed Jak1 (IFN-γ receptor associated protein tyrosine kinase) and Stat1 (transcription factor of IFN-γ). Second the antagonistic SMAD, Smad7, was switched on after administration of IFN-γ. IFN-γ also increased the level of Smad7 bound to the TGF-β receptor complex. Since Smad 3 phosphorylation and its interaction with Smad4 is a key event in TGF-β signalling, inhibition of Smad 3 binding to the TGF-β receptor complex by Smad 7 effectively down-regulates the transmission of information from the TGF-β receptor to the nucleus. IFN-γ inhibition
requires de novo protein synthesis, and was independent of MAP kinase Erk. Treatment of cells with a Smad7 antisense oligonucleotide prevented the IFN-\(\gamma\) mediated increase in Smad7 and the effect of IFN-\(\gamma\) on Smad3 phosphorylation. These results therefore demonstrated that IFN-\(\gamma\) signalling through the Jak1/Stat1 pathway rapidly increases the expression of Smad7, causing the inhibition of TGF-\(\beta\)-mediated Smad3 phosphorylation and an attendant loss of TGF-\(\beta\) signalling to the nucleus. This paper nicely illustrates the inhibitory effect of IFN-\(\gamma\)/STAT1 signalling on TGF-\(\beta\)/SMAD pathway, and may help to explain the signalling pathways that abrogate tolerance.

In the context of GI disease in man, IFN-\(\gamma\) can be seen to have two related effects. It is highly pro-inflammatory, inducing the production of TNF-\(\alpha\) and IL-1\(\beta\) by macrophages, and at the same time, it switches off homeostatic immunosuppressive pathways mediated by TGF-\(\beta\). Understanding the molecular basis for this now will allow the development of drugs which can prevent the activity of SMAD7 thereby indirectly inhibiting the inflammatory effects of interferon-\(\gamma\).

References

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Dendritic Cells,
Mucosal Immunity and Peripheral Tolerance

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A classical and fundamental question which immunologists are still finding hard to answer is how mucosal tolerance versus immunity is precisely regulated. It is far from clear, in the gut for example, what the exact regulatory mechanism or mechanisms are which determine the generation of protective immune responses to mucosally-related pathogens or harmful substances while maintaining a profound tolerance to numerous food antigens (Ag) and to normal gut flora. This has become particularly intriguing following the demonstration that dendritic cells in the gut are capable of acquiring orally- or intestinally-administered soluble antigens (Ag) and can subsequently activate sensitized T-cells in vitro and naïve T-cells in vivo.

Mucosal immunity versus tolerance: still a ‘gut feeling’

Oral tolerance, one form of peripheral tolerance, is well-recognized but poorly understood. Oral exposure to soluble Ag may result in systemic immunological hyporesponsiveness, although under certain conditions it leads to systemic priming. This appears to reflect, at least in part, the special way in which the immune system operates in the gut. Oral tolerance has therefore been suggested as one of the mechanisms to explain lifelong immunological tolerance to dietary Ag and similar mechanisms may regulate immune responses in other mucosal tissues. However, many suggested mechanisms for oral tolerance do not seem to provide satisfactory explanations. The association of oral tolerance with local mucosal immune responses, e.g. IgA production to soluble Ag remains controversial. The role of γδ T-cells in maintaining mucosal tolerance has been emphasized and TCR γδ knock-out mice have clear defects in oral tolerance, yet γδ T-cells from...
the gut may also abrogate oral tolerance. Moreover, dose-dependent tolerance (i.e., high dose tolerance) or priming certainly does not alone explain this phenomenon. Assuming that the ability of the immune system to differentiate the majority of food Ag from harmful ones is not genetically programmed, the control of mucosal responses would have to rely critically on the nature and the doses of Ag upon their initial encounter with the system. Unless mothers ensure that the food they are giving to their babies for the first time contains multiple antigens, all at high enough doses ("tolerizing" dose), systemic immune responses to these Ag upon their subsequent encounter would inevitably follow. This is clearly not the case since food allergies, which are believed to be the result of a breakdown of oral tolerance, occur only in a minority of children (2% in tolerance to cow’s milk in Europe) despite exposure to a full range of dietary Ag at various concentrations in baby food. Although the introduction of cow’s milk-based infant formula is thought to be possibly associated with a higher risk of type I diabetes, only those genetically predisposed to the disease would be at risk. Hence, mechanisms must exist at birth to regulate neonatal responses to dietary Ag that are maternally derived or contained in artificially formulated baby food. Interestingly, evidence from animal models indicates that in neonatal rats, systemic sensitization rather than tolerance may be induced after the administration of certain oral Ag. Since this inability to induce tolerance can be partially restored with adult splenocytes, it has been attributed to a regulatory imbalance in the neonatal gut. Taking together the fact that food-allergic diseases are indeed more a feature of childhood, it is obvious that such innate regulatory mechanisms also require a post-birth host maturation process.

**DC heterogeneity and functions**

Dendritic cells are not only the most potent Ag presenting cells but also the only cell type that is capable of activating naïve T-cells in vivo. It is now well established that DC acquire Ag in peripheral tissues and transport them to draining lymph nodes where processed Ag are presented to T-cells to initiate immune responses. Until recently, DC have been portrayed solely as initiators of immune responses. However there is now increasing evidence that the functions of DC are much more complex than previously thought.

DC differing in their stages of maturation, expression of cell surface markers, functional properties and tissue/organ origins have been described both in vitro and in vivo. Langerhans cells (LC) may be distinct from tissue DC and DC found in marginal zones of the spleen differ from those in T cell areas. Recently, three populations of DC have been isolated from murine lymph nodes. The most important aspect of DC classification is its relevance to their functional differences. As opposed to mature DC, immature DC are actively endocytic. This ability, which is subsequently lost upon maturation, enables them to acquire Ag in peripheral tissues effectively. DC of a mature phenotype however express highly upregulated cell surface MHC class II, as well as MHC class I, and co-stimulatory molecules such as CD80 and CD86. The latter are known to be crucial for effective Ag presentation. The difficulty with understanding the relationships between these different populations of DC arises because DC undergo dramatic phenotypic and functional changes during maturation and activation and even after short periods in culture. It is usually not clear whether identified DC subpopulations represent distinct lineages or stages of maturation within a single lineage.

In the mouse, however, it is now believed that at least two distinct lineages with different ontogenic origins exist in vivo. These comprise the “classical” DC described by Steinman, and the CD8αα DC found in thymus and other lymphoid organs that can kill CD4+ T cells in a Fas/FasL-dependent manner. In humans, CD34+ bone marrow-derived DC and peripheral blood monocyte-derived DC have been well documented although their lineage origins are yet to be defined. Nevertheless, CD4+ CD11c CD3 CD45RA+ cells purified from human tonsil have been shown to develop into DC after culture with IL-3 and CD40L (28), conditions known to give rise to lymphoid DC or DC2 in the mouse.

**Phenotypically and functionally distinct DC subsets in the gut**

Functional DC have been identified in many mucosal tissues. These include the Peyer’s patches.
the mesenteric nodes and the lamina propria\textsuperscript{2,32}; the
airway mucosa\textsuperscript{23} and the urinary tracts\textsuperscript{34}.

In rats, we have observed two phenotypically and
functionally distinct subsets of DC in lymph (L-DC)
draining the gut\textsuperscript{35}. These cells constitutively and con-
tinuously migrate from the intestine to the me-
senteric nodes. Collected under near-physiological
conditions without enzymatic treatment or incuba-
tion above 4°C, L-DC can acquire oral Ags under
steady-state conditions and present them to naive
T-cells\textsuperscript{1,2,35}. The two L-DC subsets differ in co-expres-
sion of CD4 and OX41. CD4\textsuperscript{+}OX41\textsuperscript{+} L-DC (CD4\textsuperscript{+} L-
DC for short) are stronger APC for naive as well as
sensitized T cells, and survive longer in culture. CD4\textsuperscript{+}
OX41\textsuperscript{+} L-DC (CD4\textsuperscript{+} L-DC for short) are weak APC
when freshly isolated and survive poorly in culture.
They lose the ability to process/present native Ag
completely after brief culture, but their potency as
stimulators of an allogeneic MLR is increased. One
of the characteristic differences of the CD4\textsuperscript{+} L-DC is
that they contain large cytoplasmic inclusions and
strikingly high levels of non-specific esterase (NSE).
We have recently obtained strong evidence that CD4\textsuperscript{+}
L-DC contain apoptotic cell debris derived from in-
testinal epithelial cells (IEC) and that the NSE in these
cells is derived from IEC (MacPherson et al., in prepa-
ration). Under steady conditions, CD4 L-DC migrate
into T cell areas of mesenteric lymph nodes, areas
from which CD4\textsuperscript{+} L-DC may be excluded
(MacPherson et al., unpublished data). These cells
are, therefore, constitutively transporting oral as well
as self Ag to lymph node T-cell areas - the very location
where peripheral tolerance is believed to take
place. It is of interest that freshly collected cells of
both populations appear to be DC of mature phe-
notype with high surface MHC class II and B7 ex-
pression. The lineage origins of the CD4\textsuperscript{+}and CD4\textsuperscript{+}
L-DC are however currently unclear.

Potential roles of DC in mediating self-
and oral-tolerance

Mechanisms that have been described or sug-
gested for peripheral tolerance include ignorance,
suppression, anergy caused by direct interaction
with peripheral Ag in the absence of co-stimulation,
and activation-induced cell death (AICD) involving
professional APC\textsuperscript{36,37} which is also known as cross
tolerization (reviewed by Heath et al.).\textsuperscript{18}

Aberrant presentation of Ags by non-professional
APC, such as enterocytes, lacking co-stimulatory
molecules may be one explanation for the induc-
tion of oral tolerance\textsuperscript{3} but it is difficult to under-
stand how naive T-cells which recirculate through
lymph nodes would come into contact with these
cells. Alternatively, T-cell tolerance to parenchymal
self-antigens has also been thought to be explicable
by “ignorance”\textsuperscript{38,39}. It was thus of great interest when
specific T-cell tolerance to a viral haemagglutinin
expressed as a self Ag on parenchymal cells was
shown to require a bone marrow-derived APC, rather
than parenchymal cells expressing the peptide-MHC
complexes\textsuperscript{17}. It was concluded that this type of
tolerance induction involves professional APC and
activation of T cells prior to their tolerization. In-
deed, T-cells tolerance to hen egg lysozyme ex-
pressed as self-Ag is also Fas-dependent\textsuperscript{40} and
CTLA-4 signalling by CD80/CD86 is evidently in-
volved in the induction of peripheral tolerance\textsuperscript{41}. It
is noteworthy that both the CD4\textsuperscript{+} and CD4\textsuperscript{+} L-DC
subsets in the rat are of mature phenotype by the
time they reach the draining mesenteric nodes. We
suggest that these mature CD4\textsuperscript{+} L-DC, under steady
conditions carry oral and self Ag and have direct
access to naive T-cells, and are thus able to induce
and to maintain tolerance via apoptosis\textsuperscript{42}. It would
be interesting to study the expression of functional
molecules such as FasL on these cells, particularly those
of the CD4\textsuperscript{+} L-DC phenotype.

A new model of DC-mediated self-tolerance based
on the two DC lineages identified in mouse\textsuperscript{26} has
recently been put forward formally by Fazekas de St
Groth\textsuperscript{43}. According to the theory, immunogenic or
tolerogenic properties of DC can be linked directly
to cells of the two lineages: the myeloid DC
(CD8\textsuperscript{α+}, 33D1+, DEC205\textsuperscript{lo}) being immunogenic
and the lymphoid DC (CD8\textsuperscript{α+}, 33D1-, DEC+205\textsuperscript{hi})
being tolerogenic. The important question then
becomes how these cells, or L-DC of CD4\textsuperscript{+} and
CD4\textsuperscript{+} phenotypes found in the rat, are selectively
induced or regulated? An inflammatory “danger”
signal\textsuperscript{44} mediated via DC is a possible answer.
Fazekas de St Groth’s model takes into account the
microanatomical importance of the lymphoid or-
gans, thus offering a plausible explanation as to how
DC might mediate the induction of tolerance ver-
sus immune responses: CD8\textsuperscript{α+} DC found in T-cell
areas under steady conditions are important in tolerance induction; myeloid CD8α- DC enter T areas to initiate an immune response only after they receive the “danger” signals. Thus, a germline-encoded property of these two subsets of DC with distinct ontogenic origins is now postulated to explain the DC-mediated self/non-self or normal/danger discrimination.

It has been well documented that DC migration from skin45, small intestine46 and solid organs47 can be stimulated by LPS, TNFα and IL-1. DC can be induced to migrate from hepatic sinusoids to celiac nodes by particulate stimuli48. Within the spleen, LPS or parasitic Ag induces migration of DC from the marginal zone into T cell areas49,50. Thus, another question follows: do DC remain in peripheral tissues until an inflammatory signal stimulates them to migrate? In the gut, as mentioned previously, DC are continually migrating from peripheral tissues to lymph nodes in the absence of inflammation. Two subpopulations of L-DC migrate constitutively in bovine skin lymph51. This is also evidenced by the presence of DC in all mammalian peripheral lymph sampled, including renal and hepatic lymph in normal sheep52-54. This steady state migration is presumably essential for the induction of tolerance to dietary antigens. There has to be a mechanism by which DC can migrate and introduce food Ag to the immune system without relying on inflammation. It can be argued however that, at least in the gut, this migratory process might be regulated by normal flora. To answer this definitively, further study on CD4- and CD4+ L-DC migration using germ-free animals, which have been shown to have defects in the induction of tolerance to oral Ag55, would be informative. Alternatively, inflammatory signals might modify DC properties in terms of switching from one phenotype to the other. Under steady state, CD4- L-DC are found to be the dominating cell type (about 75%) of the DC migrating constitutively in the pseudo-afferent lymph. It will be interesting to determine how the ratio of CD4+ to CD4- L-DC and their other functional characteristics change following stimulation by inflammatory stimuli.

No matter which one, or combination, of the above mechanisms is responsible for the selective induction of DC mediated tolerance versus immunity, a process of dynamic balance within the immune system is clear — another example explained perfectly by the ‘Ying/Yang’ theory. Upon stimulation by bacterial products, the so-called myeloid DC have been shown to enter T-cell areas, but an early increase in lymphoid DC in the same areas is also evident49. Similarly, in response to LPS or parasite extracts (e.g. Toxoplasma gondii) most of the activated DC (CD11c+), as indicated by IL-12 expression, detected in T-cell areas were of CD8α+ DEC-205hi phenotype50, although it was not clear how the cell ratio between CD8α+ and CD8α- might be changed. Cytokines are likely to be the mediators for the reciprocal control of DC and T-helper cell differentiation29. New evidence has emerged indicating that differential regulation of immunity and tolerance is associated with a balance of signalling between CD80 and CD86 respectively, and such a balance is also reciprocally controlled by Th1 and Th2 cytokines29. With the recent finding of HLA-G, a tolerance-related MHC class I molecule which is expressed on DC and can be regulated by IL-10 and IFN-γ57, there is little doubt that DC, apart from their role in initiating protective immunity and in central tolerance, are also crucial mediators of many forms of peripheral tolerance by providing a close but highly regulated link between innate and adaptive immune mechanisms.

Acknowledgement

We wish to thank Emma Turnbull for her helpful discussion and critical proof reading.

References

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Mucosal Immunology Workshop–Harrogate 1998

After an exhausting week at Harrogate it was a
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Mucosal Immunology Affinity Group Workshop–
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Interactions between innate and acquired
immunity at mucosal surfaces

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peptides by Ray Playford from Leicester. These are a
family of 3 very interesting small peptides made by
epithelial cells whose main feature is their ability to
promote epithelial restitution after gut injury. They
will shortly be going into patients to determine if
they promote ulcer healing. This was then followed by a talk by Ian Sanderson from Bart’s on chemokine production by gut epithelial cells and its modulation by nutrients and gut bacteria. Ian described the transgenic mouse that Yoshi Otsuka has made in his lab where MIP2 is overexpressed in the gut epithelium using an epithelial specific promoter. The final talk before coffee was an excellent review by Charles Parkos from Emory who covered all of the work he and Jim Madara have done on identifying the epithelial surface ligands which neutrophils recognise as they bind to and cross the gut epithelium. In addition he covered the functional work where it has been shown that adenosine secreted by neutrophils in the gut lumen is the stimulus for secretion of ions by gut epithelia. These studies have direct relevance to the diarrhea seen in diseases such as ulcerative colitis, amebiasis and shigellosis where neutrophil recruitment into the gut is a prominent feature. The morning session ended with a technicolor feast of pictures by Per Brandtzaeg from Oslo who covered the expression of homing molecules by gut cells, as well as some of his work on the function of gut endothelial cells. As the world's best at multi-color immunofluorescence on tissue sections, Brandtzaeg’s work now resembles a mixture of Jackson Pollock meets Roy Liechtenstein, the latter by the fact that the colors are now so complex that he has to provide multi-color cartoons to explain to the audience what they are seeing. Seeing these pictures though, few could dispute that α4β7 is the gut homing molecule in man.

At lunch the affinity group held their AGM and it was decided that Kingston Mills would organise next year’s symposium, with more focus on the lung. This is particularly appropriate since next year’s meeting is with the allergists.

The afternoon session was more sparsely attended, as people departed Harrogate. However as the audience got smaller, the talks got better and the session was one of the best I have ever attended. First of all, Hugh Miller showed a lot of new data on the control of protease production by mucosal mast cells. He showed clearly that TGFβ is the key cytokine responsible for protease upregulation in these cells, reinforcing the message that it is a key cytokine at mucosal surfaces. Gordon Dougan then gave a memorable talk split into 2 sections. In the first half he covered current work by Gad Frankel and himself on intimin of enteropathogenic E. coli (EPEC). When these bacteria infect the gut they inject a receptor into gut epithelial cells to which intimin on EPEC then binds. The structure of intimin has just been solved by NMR and although a bacterial protein, it has a terminal C type lectin domain and 2 Ig-like loops. In the second part of his talk he covered the use of non-toxic mutants of cholera toxins as oral adjuvants—the great unfulfilled promise of mucosal vaccination. The final presentation before coffee was a magnificent talk by K-E Magnusson from Sweden who covered his studies on the way in which the protease from Vibrio cholera could degrade epithelial tight junction proteins.

In the final session the high standard was maintained and even exceeded. Delphine Guy-Grand from Paris gave an amazingly good talk on mouse intraepithelial lymphocytes, covering every aspect of their origin and function and making those in the audience who also work on IEL wonder why they bother. It was really a tour de force and it was somewhat regrettable that Delphine had booked a cheap flight home necessitating a Saturday night stay in Harrogate, something that none of us would wish to suffer. The short straw for the last talk fell to Jo Spencer from St. Thomas' Hospital who wisely realised that V region sequences and somatic hypermutation in gut B cells were beyond the capacity of a tired audience. However in her sophisticated molecular analysis she showed that it was very unlikely that there was a B1 lineage of cells in humans, unlike mice, because all human IgVh genes in the gut, regardless of isotype, are highly mutated. Thus there are no natural antibodies encoded by germ line genes in human gut. The session wound up, on time, with 50 dedicated souls remaining to the end.

Overall the session was a success although we probably failed in our aim of interdigitating innate and acquired immunity in the gut. Nonetheless most of the talks were very good and some were quite superb (even the non-immunologic ones like Dougan and Magnusson). There clearly is a great deal of interest in mucosal immunology and the standard of talks deserved a bigger audience. Coming at the end of a tiring week is not the best time to have such meetings and so in the future we will try to run them earlier.

Tom MacDonald
St. Bartholomews Hospital
The First European Mucosal Immunology Meeting

“People will come!” And to the surprise and delight of the Mucosal Immunology Affinity Group, who organized this meeting, they certainly did. The Group first identified the need to co-ordinate the field within Europe some three years ago, and, on 2nd and 3rd of October, 270 participants from 17 European countries finally met at St. Bartholomew’s Hospital in London. The level of enthusiasm for the topic can be judged by the fact that there were over 400 applications to attend, but this had to be limited to 270 because of the size of the venue. Attendance was on a first come-first served basis. An impressive list of international speakers was assembled, who were happy to pay their own expenses to the meeting. In addition, there were 45 poster presentations and 16 short oral presentations of submitted abstracts, all of a very high standard. Based on the theme “The cells and molecules important in mucosal tolerance and inflammation”, the First European Mucosal Immunology Meeting addressed the vital questions: What maintains mucosal immune homeostasis and what causes its breakdown in inflammation?

At the first level of interaction of antigen with the mucosal immune system, new light is being shed on the control by B cell products of the differentiation of antigen sampling epithelial M cells overlying Peyer’s patches from absorptive epithelial cells (N. Debard, Switzerland). Exciting new work is showing the active participation of the epithelium in directing the mucosal immune response and responding to antigen by altered gene expression (I. Sanderson, UK; R. Hershberg, USA). The induction of an appropriate immune response to antigen following its interaction with the epithelium is to a large extent dependent on the nature of the mucosal antigen presenting cell (M. Bailey, UK) and modulation of responses can be achieved by targeting alternative processing and presentation routes using cholera toxin (N. Lycke, Sweden).

Downstream of the first interactive events with antigen and dependent on the route of entry, and the concentration and the structure of the antigen which passes the epithelial barrier, the response is regulated by T cell anergy or suppression (A. Mowat, UK). Specific interactions between developmental signalling receptors, such as Notch, and their ligands on naive and regulatory T cells (G. Hoyne, UK) may provide the molecular key to understanding the regulation of mucosal responses. IgE mucosal responses are differently regulated from IgG responses (G. Kraal, Netherlands). It is perhaps not surprising, then, that the window of antigen concentration which permits successful induction of tolerance, both in experimental models and in recent human trials, is very restricted (G. Panayi, N. Staines, UK). The capacity of cells to lodge in the gut mucosa is controlled by unique gut-homing adhesion molecule profiles expressed on Peyer’s patch lymphocytes (I.N. Farstad, Norway; A. Hamann, Germany) and the subsequent homing of activated cells to effector sites in turn depends on the site of induction (M. Quiding-Jarbrink, Sweden).

The mucosal immune response to luminal antigens is tightly regulated and when things start to go wrong, as in chronic inflammatory bowel disease, TNF-α is at the centre of things. From its role in regulating apoptosis in the mucosa (M. Boirivant, Italy), to its multiple actions in full-blown Crohn’s disease, its importance is revealed by the success of anti-TNF-α antibody treatment of Crohn’s disease (T. ten Hove, Netherlands). Recent work defining regulation of TNF-α-induced signalling and activation mechanisms (M. Neurath, Germany; F. Pallone, Italy) and the emerging understanding of regulation of TNF-α transcription through repressor elements (S. Schreiber, Germany) will point the way to more specific therapies of mucosal inflammation. Equally, analysis of the complexities of the inflammatory process using model systems such as the CD4+ T cell-transplanted SCID mouse (F. Powrie, UK; J. Reimann, Germany), or the CD3e transgenic model (S. Simpson, Ireland) shows great potential for defining anti-inflammatory therapy. The vital interaction between genetic and environmental fac-
Charles Elson, M.D.

is Professor of Medicine and Microbiology and Director of the Division of Gastroenterology and Hepatology at the University of Alabama at Birmingham and he holds the Basil I. Hirschowitz Chair in Gastroenterology. Dr. Elson received his undergraduate degree from the University of Notre Dame and his M.D. from Washington University School of Medicine in St. Louis. He did his clinical training in internal medicine and gastroenterology at Cornell University and the University of Chicago. Following that he worked for four years doing basic immunology research at the National Institutes of Health in Bethesda Maryland mainly in the Immunology Branch working with Dr. Warren Strober. While at NIH he provided some of the first direct experimental evidence demonstrating IgA-specific T cell regulation. Subsequent work in mucosal immunology has centered about regulation of mucosal immune responses, much of it using cholera toxin as probe. These studies led to the first observation that cholera toxin can act as a mucosal adjuvant; the mechanism of such adjuvanticity has been the focus of a number of subsequent studies.

During his Fellowship in Gastroenterology he developed an interest and research focus into inflammatory bowel disease that has been a continuing theme for the past 20 years. In recent years this has taken the form of development of experimental mouse models such as the C3H/HeJ Bir mouse, which develops colitis spontaneously under certain conditions. Recent published studies demonstrate that CD4 T cells reactive to commensal enteric bacterial antigens mediate this colitis.

Dr. Elson maintains an active clinical practice providing consultative care to patients with gastrointestinal disorders, particularly inflammatory bowel diseases. He has served on numerous foundation and NIH study sections and advisory panels and currently is Chairman of the Grants Council of the Crohn’s and Colitis Foundation of America. He is a member of a number of national organizations including the American Association of Immunologists, American Society of Microbiology, American College of Physicians, and has recently been elected to the Association of American Physicians. He is a co-founder of the Society for Mucosal Immunology and served as its first Secretary-Treasurer. With this extensive background in mucosal immunology, we all look forward to his leadership as President of the Society for Mucosal Immunology.

New President for SMI

Charles Elson, M.D.

First EMI, continued from page 17

itors, both in maintaining immune homeostasis in the mucosa and in the pathogenesis of mucosal inflammation was elegantly stressed by Balfour Sartor (USA) in the closing keynote lecture.

Plans are already afoot to build on the success of this meeting by establishing regular European Mucosal Immunology meetings, with the next tentatively planned for 2000 at a venue outside the UK. The success of the meeting was due to a number of factors. It was very focused and there was no registration fee. The willingness of senior figures to attend at their own expense to attract participants was undoubtedly important. Flights into London are good and the meeting was held at a central location, easily reached from all London airports. The meeting started on Friday afternoon and ended late Saturday afternoon so that participants could get cheap flights, flying in Friday morning and leaving on Sunday. Reasonably priced hotels were identified for the participants. The social event on Friday evening was a great success. Finally, there was tremendous support from the BSI, Society for Mucosal Immunology, Astra Hassle, Cantab Pharmaceuticals, Pfizer Inc., and Centocor. We hope that this is the first of many.

Paul W. Bland, Allan Mcl. Mowat, Thomas T. MacDonald
Mucosal Immunology Affinity Group, BSI
## Society Business

- Recently, the Governing Council approved the suggestion by Drs. Kagnoff and Kiyono to create an educational fund in support of mucosal immunology in developing countries. The goals of this fund are to facilitate the development of educational efforts in these countries. Currently, the priorities are to increase the cash available to support these efforts, hence, a request for contributions from members was included in your renewal notices. Interested individuals are asked to seek contributions from industry, government, or private foundations to augment the fund as well as provide suggestions for their use. Consider action of requests for projects will begin in 1999. Please contact the Secretary-Treasurer, Peter Ernst, at the Society Business Office with your suggestions and requests.

- Recently, members should have received their new SMI Membership Directory. With the increase in new members that the 10th International Congress for Mucosal Immunology has attracted, we plan to publish an updated edition early in 2000. Please carefully read your description in the directory. If any information is incorrect or missing, forward the corrections on to Mr. Peno by email at smi@paimgmt.com.

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### Announcements

#### Society for Mucosal Immunology — Application for Membership

Membership in the Society for Mucosal Immunology is open to all immunologists, physicians, dentists, veterinarians, biochemists, or other scientists who do research in or who have an active interest in mucosal immunology, and who have published at least one first-authored paper in a peer-reviewed journal. Society membership includes a subscription to Mucosal Immunology Update.

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Please mail completed application form with $10 application fee and $60 annual dues (total $70) payable by check in U.S. dollars or by VISA or MasterCard account number (please include expiration date and MasterCard 4-digit interbank number) to Dr. Peter Ernst, Secretary-Treasurer, The Society for Mucosal Immunology, 4340 East West Highway, Suite 401, Bethesda, MD 20814-4411, U.S.A. Or e-mail to smi@paimgmt.com.