to raise the attractiveness of Europe to draw scientists from other parts of the world; and to raise the overall level of research investment in Europe. An ERC that is just a funding mechanism might not be able to achieve this. It was Iain Mattaj, present Scientific Director and the designated Director General of the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, who asked whether an ERC should fulfil a further role: that of formulating a European research strategy?

It is still not clear what the legal setting for an ERC will be—whether as an executive agency of the EC … with a governing board of representatives from national governments, or as a new truly European institution

At present, there is clearly no such strategy. Science policy is formulated in Berlin, London, Paris, and other capitals, and to some extent at the EC, but none of these take a truly international outlook on basic research, on the career and job prospects of scientists across Europe, on the role and function of large European research infrastructure and facilities (such as EMBL, the European Laboratory for Particle Physics (CERN) and the European Space Agency), and on how to remove hurdles to the mobility of researchers. The successful creation of an ERC might prompt European scientists to push for even greater change, as they realize that they can make a difference. As José Mariano Gago, Chair of the ISE and a former minister of research and technology in Portugal, summarized, "Science policy has entered a new state," which is increasingly driven by the scientists themselves. Catherine Dargemont, President of Sauvons La Recherche (Let's Save Research), the organization that forced the French Government to take back its announced cuts to science and research earlier this year, reassured the audience that if there is a will, there is a way: "As scientists we should not underestimate our capacity to influence our politicians."

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Should auld acquaintance be forgot…

The 'hygiene hypothesis' is less about cleanliness, and more about the changes that humans have made to their lifestyle

In 1989, David Strachan from the London School of Hygiene and Tropical Medicine, UK, proposed an intriguing explanation for the sudden rise in hay fever and allergic diseases in developed countries during the previous few decades. His theory, later nicknamed the 'hygiene hypothesis', linked allergies to hygiene and household size. Based on observations that children in large families were less likely to develop hay fever than those with fewer siblings, Strachan declared that "declining family size, improved household amenities and higher standards of personal cleanliness" had all decreased the number of infections that children contracted, which might have led to more allergic diseases (Strachan, 1989). Before long, his hypothesis became synonymous with the belief that the trend towards better hygiene and cleanliness was the main cause for the relatively recent emergence of asthma, hay fever and other allergies.

… the time has come to rethink, and rename, the hygiene hypothesis

At that time, immunological research seemed to support the idea that a naive immune system—that is, one that was not permanently challenged by infectious or parasitic organisms—was likely to overreact to more benign objects in the environment. Work over the past 15 years, however, has revealed that the real picture is much more complicated. Recent research indicates that the risk of developing allergies is not necessarily caused by a lack of bugs and parasites in the environment *per se*, but rather by a lack of certain organisms that have, over the course of evolution, trained our immune system be more tolerant. This suggests that the time has come to rethink, and rename, the hygiene hypothesis.

When researchers first tried to understand the link between infectious and allergic diseases, it seemed logical to focus on one particular component of the immune system: T-helper (Th) cells. Th1 cells normally fight bacterial or viral infections, but also have a role in autoimmune disease. By contrast, Th2 cells deal with parasitic infections and mediate allergic reactions. Allergy researchers initially believed that reduced exposure to microorganisms failed to prime the Th1 response, which then led to overcompensating Th2 activity and resulted in allergies. However, "at exactly the same time, a smaller number of people working in the field of autoimmunity, where diseases are of course mostly mediated by Th1 lymphocytes, were producing the reverse hypothesis," said Graham Rook, a professor at the Centre for Infectious Diseases and International Health at the Royal Free and University Medical School in London, UK. "They were actually saying there's not enough Th2 activity around now, we need more Th2 to downregulate the Th1 that's causing multiple sclerosis, type 1 diabetes, and Crohn's disease." In fact, while allergy specialists had been preoccupied with explaining the sudden rise of asthma and allergic disorders, the prevalence of autoimmune diseases, such as multiple sclerosis, type 1 diabetes and inflammatory bowel disorders, had risen just as dramatically.

This, in turn, put paid to the theory that Th2 cells were directly responsible and prompted researchers to look elsewhere. "What one needs is a hypothesis that can explain a simultaneous increase in Th2-mediated diseases, Th1-mediated diseases and also inflammatory bowel disease, which is mostly Th1-mediated but possibly

ulcerative colitis with a smidgen of Th2 as well," explained Rook. "And of course there's also an increase in food allergy, which is rather a different issue from other sorts of allergy. These things are all increasing. What they have in common is that there are targets that the immune system should not be attacking, and those targets are self, gut content and trivial amounts of the neighbour's cat wafting past in the breeze."

Instead of focusing on the Th cells themselves, researchers turned to regulatory T-cells and their role in controlling Th1, Th2 and unwanted immune responses. "What is exciting now is that if you look at people with these various [allergic and autoimmune] diseases, it's becoming quite obvious that they do indeed have deficits in regulatory T-cell activity," Rook said. "I don't think that anyone seriously believes the Th1/Th2 see-saw anymore in relation to the hygiene hypothesis," he added, pointing to data that show a positive association between the simultaneous occurrence of type 1 diabetes and asthma both within and outside Europe (Stene & Nafstad, 2001).

However, this new insight does not explain why allergies and autoimmune diseases are on the rise nearly everywhere in the developed world. Because their prevalence has increased markedly over a relatively short period of time, the underlying cause cannot be attributed to the slow pace of evolution—

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rather, external, environmental causes are most likely. Hygiene seemed to be a likely culprit; after all, our move to chlorinated water, cleaner air, modern sanitation and improved personal hygiene happened at about the right time. Yet it is not clear how this affects immunity. "The first question is, is microbial exposure important for a balanced immune system, and then the second question is, if reduced microbial exposure is important, what types of microbial exposure and why has it changed?" asked Sally Bloomfield, an honorary professor at the London School of Hygiene and Tropical Medicine, UK, and co-author of a recent report from the International Scientific Forum on Home Hygiene (IFH) that reviews the hygiene hypothesis (Stanwell-Smith & Bloomfield, 2004). According to Bloomfield, "There's a whole load of things that could have altered the way in which we interact with microbes."

Rook has his own theory about how the interactions between humans and microorganisms have changed. He has identified various 'old friends'—microorganisms that were once abundant and harmless, but are now absent from everyday life, thanks to changes in our lifestyle over the past century. Lactobacilli, saprophytic mycobacteria and some parasitic worms, or helminths, top the list, although there are probably many more. "What I think is so interesting about the helminths is that they really have disappeared from our environment. In Europe it was probably the pinworm that was the last one to become really quite uncommon and that happened at about the right time for these massive increases [in allergies] in the 60s and 70s," Rook said. "Similarly, we just don't get saprophytic mycobacteria in our chlorinated water supplies anymore, whereas they would have previously been enormously common."

According to Rook, it is the disappearance of these 'old friends' that might cause allergies and autoimmune diseases, because their presence used to teach our immune system not to react to everything that it came across. Once a helminth invaded the body, the immune system would be so overwhelmed with having to fight something of that size that it simply tolerated its presence through massive immunoregulation. Many other organisms in the human gastrointestinal tract, such as lactobacilli, are in fact beneficial for gut flora and so the immune system has come to overlook their presence during the course of evolution. "The 'old friends', as we call them, are all either things that really do us no harm, or things where the immune system is forced to give in and avoid a fight because it's just a waste of time," explained Rook. Learning how to tolerate such invaders might therefore teach the immune system a valuable lesson on when not to react to foreign matter. "People get the immune system the wrong way around. We're so focused on the immune system responding to things, that we forget that 99.999% of the time, its job is to not respond to things. There's you and your breakfast and your gut, for a start. That's a lot of stuff to not respond to."

This leads to the question of how the immune system learns to tolerate these invaders. Leonid Margolis, the Deputy Director of the National Aeronautics and Space Administration (NASA)/National Institutes of Health (NIH) Center for Three-Dimensional Tissue Culture at the National Institute of Child Health and Human Development (Bethesda, MD, USA),

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believes that a more detailed classification of microorganisms is needed to show how various pathogens interact with the human body and *vice versa*. "Since each of these microbes pursues its own strategy, you find that what is beneficial for one microbe can be detrimental for another," Margolis said. His laboratory aims to identify microbes that create conditions that are unfavourable for important human pathogens, such as the human immunodeficiency virus (HIV). However, controlling the same networks in the immune system might also affect diseases that are not linked to pathogens, such as autoimmunity and allergies. Margolis has suggested the creation of a 'periodic table' of microorganisms, in which the effects of various microbes on the immune system are systematically catalogued (Margolis, 2003). This would help allergy researchers to identify the microorganisms that increase the tolerance of the immune system. "Even if this hypothesis is proven, the strategy will not be to abandon hygiene, but rather to understand the molecular mechanisms underlying the phenomenon," he warned with regard to quick conclusions. "When and if this happens we will find ways to trigger the same mechanisms with targeted drugs rather than by natural infections."

Rook and colleagues have already shown encouraging results from preliminary trials in which asthmatics were given heat-killed mycobacteria (Camporota *et al*, 2003), although further clinical trials are required. Joel Weinstock, a gastroenterologist at the University of Iowa (Iowa City, USA), and colleagues have also shown that feeding helminths to patients with inflammatory bowel disease can downregulate intestinal inflammation and even temporarily push the disease into remission (Summers *et al*, 2003). Pharmaceutical companies, however, have not shown overt interest, regardless of the potential market for anti-allergy medications. "They're very much now oriented towards the magic bullet thinking," Rook explained. Innate immunity involves hundreds of different receptors and specific pattern recognition for each foreign substance, so it might not be possible to mimic it with single molecules. "If you've got to find a whole number of different molecules which together produce the pattern that gives the appropriate signal, that would be a nightmare to do molecule by molecule, from a drug development point of view," Rook said.

Learning how to tolerate such invaders might therefore teach the immune system a valuable lesson on when not to react to foreign matter

Instead, he is placing his bet on the food industry, based on his finding that the oral administration of the 'old friends' is effective and that the required doses might be easy to add to foods. Companies, such as Danone (Paris, France) and Yakult (Tokyo, Japan), known for their probiotic milk drinks that are marketed to promote their beneficial bacterial content, have already expressed an interest. Incorporating the 'old friends' into food products could therefore become a new type of 'vaccine' against faulty immunity. "It's not that vaccines [against microorganisms] are doing any harm," Rook said. "I think that we need new kinds of vaccines that are not targeting any specific infection, but are targeting immunoregulation."

Many of the details still need to be ironed out before a probiotic drink that reduces allergy risk is available in supermarkets. "I wouldn't say it's the perfect answer to everything," Rook said about his 'old friends' mechanism, "but it's at least good enough to provide the final piece of the logical chain of arguments. One has the epidemiology, one has the animal work, and one now has the clinical results. It hangs together pretty well." What is needed is collaboration between the various research fields that are involved in identifying the links between these arguments. In the past, this was largely hindered by the fact that allergy researchers and infectious disease biologists rarely worked together, even though both focus on the same topic: the human immune system. Bloomfield also pointed out that it might be difficult to assess and discuss the role of hygiene in allergies and autoimmune diseases, because so many different agencies oversee home, water, sanitation, air and food hygiene.

Despite these difficulties, almost all of the scientists agree on one thing: the use of the word 'hygiene' is misleading and confuses the role of cleanliness in the development of the immune system. To allay public fears and avoid confusion, not to mention to more accurately reflect the nature of the hypothesis, many have called for a new name. "I think it's a good idea because 'hygiene hypothesis' for the general public may suggest that we should abandon hygiene, and that what we have developed over centuries—all the efforts of all medical researchers and doctors—is wrong and should be dropped," Margolis said. The suggestion made by the IFH, the 'microbial exposure hypothesis', and Rook's 'old friends' moniker therefore return the focus to the role of the microorganism in educating the immune system. As Rook explained, "What we're talking about really is fundamental changes in lifestyle, it's not just the trivial matters of everyday domestic hygiene. It's the fact that we no longer drink water from the stream and we no longer have worms."

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