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Systematic and systemic immunology: on the future of research and its applications

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Abstract This paper is a shortened English transcription of a lecture given on 13 February 2012 at the College de France. The lecture concluded a series of talks delivered the same year on the theme: "Immunity: the game of chance and specificity". The article comprises four parts: I. The game of chance and specificity. II. About the future of research in immunology. III. On the future of the applications of research in immunology. IV. The social conditions of the evolution of research and its applications.

Keywords Evolution · Systems biology · Immune system · Cellular networks · Complexity

Ladies and gentlemen,

This is the last lecture of the series entitled: "Immunity: the game of chance and specificity". I do not intend to summarize what I explored with you in the previous eight talks [1], but rather I wish to provide you with a number of considerations about the future of the discipline as I see it in the social frame of its evolution.

A few considerations about immunology and its future

The game of chance and specificity

While echoing Jacques Monod's book "Chance and necessity" [2], my thinking about "chance and specificity" is profoundly different. It primarily relates to biological function rather than evolution, even if evolution provides the underlying landscape, together with the theological flavour, that Monod emphasized. The theme of chance and specificity permeates the whole of biology, but it is particularly important in the immune system (IS). The IS defends organisms against external infectious agents and a number of internal disorders and hazards, all of which occur randomly. So, chance is ubiquitous, and specificity refers to the degree of precision with which immunological processes cope with chance events.

Specificity cannot be perfect, and, systematically, chance is not "absolute". This statement means that, at the various levels of organization of the IS in complex multicellular organisms, randomness is canalized, as illustrated by the architecture of the thymus, spleen and lymph nodes. In these lymphoid organs, cellular traffic is organized as a means to constrain randomness to an extent that makes specific recognition events happen in an "acceptable" time frame. The time needed to elicit a new immune response involving naïve B and T cells would be much too long if it occurred purely by chance. As for immune specificity, it only rarely follows the "lock and key" paradigm of enzymatic reactions, which we were often taught in the past. Rather, it is usually a combination of relatively loose processes that ends up reaching the appropriate level of specificity. These features hold true across the molecular, cellular and multicellular levels of a multilayered organization. The game of chance and specificity is not a gamble: it is a negotiation

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arbitrated by functionality, which results in compromises and trade-offs. Extreme specificity is unaffordable, and extreme chance is unsustainable. Evolution has selected a variety of mechanisms that cope with these limitations.

Inherent in life is the dialectical relationship between predators and prey. Infectious agents are microscopic predators against which hosts have evolved a vast number of defensive mechanisms. Bacterial DNA restriction and modification provides a primitive example that evolution has not taken much further, contrary to phagocytosis which is a general mechanism. Defence systems are tailored to their hosts: thus, plants, which do not have circulating cells, have evolved mechanisms distinct from animals.

Innate immunity can be viewed as an accumulation of relatively specific mechanisms piled one upon another. Adaptive immunity, in principle, provides a more general mechanism suited to the recognition of any pathogen or "foreign" object. In animals, it emerged through three major innovations: composite genes (randomly generated by gene recombination and/or conversion); composite proteins (namely MHC molecules loaded with peptides or lipids); and statistical sampling of the intracellular milieu and extracellular environment. These mechanisms alleviate size limitations of the genome and spatio-temporal constraints in the organism (since everything cannot be displayed everywhere at the same time). Overall, they are efficient enough to saturate the realm of possibilities, since experience shows that there are few or no holes in the repertoires dealing with immune recognition.

Both pathogens and the IS of any given organism are under strong mutual selective pressure. To illustrate this point, I invite the reader to examine the MHC-I and II presentation pathways, and note that virtually, every known step in these processes is the target of at least one escape mechanism evolved by at least one pathogen. On evolutionary grounds, it is remarkable that adaptive immune systems have emerged (at least) twice in two distinct biochemical and cellular forms, as illustrated by the lamprey's VLRs. An adaptive form of the IS, on top of, and combined with innate immunity, is expected to control more infectious agents and/or it may be important to fight highly variable pathogens (Plasmodia, flu virus, etc.), or perhaps to cope with the diversity of food. Innate immunity can also be viewed as being ascribed to an ecological niche, while adaptive immunity might be better suited to a variety of niches and to animal mobility. Adaptive immunity has also, by its very nature, allowed better surveillance of the internal milieu, in addition to that of the environment. It participates in the control of random genetic and epigenetic defects and of various dysfunctions, a role which is now recognized as increasingly important.

About the future of research in immunology

In my previous lectures, I have already alluded to several topics that I deem important for the future, some of which I discuss below.

First, the issue of topology is, in every respect, essential, because, in my view, random diffusion is likely to be extremely limited within the intracellular milieu. Topology is also key to the interactions between immune cells, as well as in the circulation of cells, and in functional immunity within organs. Thus, functional anatomy should be studied more. Secondly, there is a need to further study the IS in the context of the rest of the organism, in particular to understand its integration with metabolism and energy supply, as well as with the endocrine and nervous systems. For example, circadian immunology is on the rise. Neuro-immunology is bound to make considerable progress, and neuro-psycho-immunology has begun to yield scientifically credible results. I also believe that physics should be given greater consideration. Immunological thinking must call more on the basic notions of force, shape and its distortion, speed, flux, etc. Time and kinetics are fundamental in immune responses, which altogether too often are studied from a static standpoint. Finally, all experimental sciences develop a synthetic arm as they mature; it has so far been the case with physics, chemistry and genetic engineering. At the molecular level, immunology has started growing a synthetic branch, and it will be interesting to see whether and how it develops at the cellular level. The advances in technology that permit synthetic research will play a major role in the future in enabling us to tackle what is, in my opinion, the most compelling issue facing immunology research today—that of complexity.

Complexity and the future of immunology

Historically, physics has helped biology to renounce vitalism. Molecular biology and molecular genetics have driven major advances, initially based upon a reductionist approach, which has allowed the analysis, in considerable detail, of individual genes and proteins. Technical progress leading to the acquisition of massive amounts of data has now enabled us to go beyond this reductionist phase. The sequencing of the entire human genome about 15 years ago has become the totem of this inflexion. From that time on, complexity has revealed itself as a major intellectual and scientific challenge, in biology at large, and in the IS in particular. It was obviously suspected to be very complex, but the tools were previously lacking to dig into this complexity, leaving us with a "black box" approach as the only option.

Immunology is currently becoming **systematic** rather than systemic. Systematic immunology involves a distinct mindset: if, in a given experiment, I wish to measure one cytokine, I may decide to measure them all, even if this does not appear immediately necessary or important. When doing so, I may or may not find something unexpected or interesting, but I will have dealt with the question of cytokines exhaustively. Then comes the question of how I am going to store these data and whether I will keep them for myself or make them accessible to others, even if they are not used in my publication. Immunology is bound to become still more systematic in the future as the available technologies increasingly make it so.

In my view, technology does not always receive the recognition it deserves. There are periods during history in which technology was strongly pushing, if not fully driving, science. With the acceleration of DNA sequencing, we shall soon need a "Google" of human genomes. In protein research, major advances are happening in terms of prediction of structures, dynamics of conformations, and, most importantly, in the structural analysis of more and more complex, even loose, molecular aggregates. Chips of all sorts are commonly used to determine transcriptomes, proteomes, metabolomes, liposomes, etc. Cell sorting associated with mass spectrometry [3] is probably a breakthrough. Imaging is making considerable progress in the mouse, although remaining more difficult in man; this will make advances substantially harder for human immunologists.

Complex systems

The transition between systematic and systemic immunology resides in the description and understanding of complex systems. Complexity is rooted in philosophy, engineering, informatics, social networks and biology, more than in the mainstream of physics. A gas, such as the air we breathe, is made up of an enormous number of molecules, but they are of a very few types, and display but a few types of interactions. Accordingly, a gas is not a complex system. A clock is indeed complicated, but is not a complex artefact, because its elements interact in an almost linear way. On the contrary, unicellular or multicellular organisms are made of numerous different elements with many distinct interactions. This feature is characteristic of complex systems, in which the notion of "distributed property" refers to properties of the system that cannot be assigned to, or understood from, a small number of elements and/or interactions. Robustness and its counterpart, fragility, are distributed properties of complex systems. Robustness is the ability of the system to go on working irrespective of unexpected variations in its environment or its internal functioning. By this definition, biological systems are claimed to be very robust; in this respect, robustness is not foreign to the theme of chance and specificity. The functioning of a robust system looks simple because many dysfunctions are masked. Thus, robustness may hide complexity, and complexity has to be specifically investigated to be fully appreciated.

How can one estimate the degree of complexity of a network? The easiest, but perhaps too simplistic, approach is to count the number of elements and interactions (nodes and edges in the network). A more sophisticated route is to analyse the controllability of networks. Thus, Liu et al. [4] have evaluated the proportion of "driver nodes", that is, the ones that must be controlled in order to be able to shift the entire network from any given state to any other. A comparison of 37 published networks of very different origins (electric grids, mechanic devices, and informatics, social and biological networks) shows that, by and large, biological systems are the most complex of all, with about 80 % of the nodes being "driver nodes" [4]. Interestingly, this fits a number of experimental data, such as those obtained with the protein networks of drosophila [5].

In ordinary language, this suggests that biological networks are extremely intricate, such that changes almost anywhere in the network may have an effect elsewhere. This, in turn, raises the important issue of **modularity**. How can one identify relevant subsets that can be abstracted from the system and define practical modules with which one can think and do experiments? This problem is different in the two fields of life sciences and mechanics, for example. In the latter case, the assembly and operational manuals are, in principle, available. In addition, if one takes a car, it is clear that a door, a rear-view mirror, the bonnet, etc. are identifiable and separable modules. There is no such clarity in biological systems. First, the deconvolution exercise from the available data is of a different nature, and heavily dependant upon annotation. Secondly, it is not clear that modules (such as a transduction cascade) are truly identifiable and/or separable.

This reality holds at all levels of organization of the IS. The immune cell is, as of today, the most pertinent and best explored of these levels, and also where systems immunology currently merges with systems biology. The next step should be the analysis of subsets of interacting cells. For example, the tools are still lacking to simultaneously analyse a pair of cells (such as a dendritic cell and T lymphocyte), fully deconvolute the information relevant to each cell and follow the kinetics of the interaction. At a higher level, an inflammatory site constitutes an amazingly complex system, since many cell types assemble, with all sorts of cytokine- and chemokine-mediated interactions alongside specific cell–cell contacts. It is likely that certain polarized cells can substitute for others, with the same inflammatory output, as postulated in the cytokine field theory that I have previously proposed [6].

Altogether, we face a triple heuristic change. First, the dialectical relationship between making experimental observations and formulating hypotheses has been modified; systematic immunology prompts us to make a series of blind observations first, and to delay the definition of the hypothesis. The second point is that hypothesis-driven immunology, in a systems approach, has to cope with the definition of modules. This is a mental operation in which the experimenter abstracts out of the entire system what he believes to be a relevant subset. To put it in different words, the observer introduces into the system as much as, and, perhaps, more significance than he or she finds through observations. As a consequence, in the absence of demonstrated physical reality, the major source of validation of biological modules relies upon discussion and agreement between experts in the field. Note that the IS is an example of such an abstraction, which leads many immunologists to neglect its links with the rest of the organism, metabolism being an obvious example.

We are also confronted with a change in heuristic behaviour. Faced with massive amounts of data, the human mind finds its limits long before the computer. In my view, the chess battle won by the computer Deep Blue over Garry Kasparov in 1996 was a historical turning point. The limits of appreciation of complexity by the human mind have been revealed. Incidentally, this is also true of the scientific literature, which now needs to be "modelized", as achieved by the writing of scientific reviews—a shift made evident by the success of journals devoted to that purpose. Regarding immunology, there are tens or hundreds of specialized databases, not all compatible with one another, and a variety of computational approaches [7]. Aimed at building descriptive and hopefully predictive models, it must be kept in mind that such models heavily depend on the quality of the data, and are too often static. Also, as we well know, models are worth only what we put into them, and the hope of large scale deconvolution is often misconceived [8].

Material elements, virtual links and distributed properties in multilayered complex systems

The description of a complex system starts with that of its constitutive (material) elements as well as that of the (virtual) links that relate these elements according to certain rules. An interesting output of engineering sciences is that (virtual) rules often appear more important than the (material) elements [9]. Put it this way: it is often easier to change a nut and bolt than its location in an artefact, because modifying the latter may disturb the equilibrium of the network.

This vision is significant for immunology in several ways. First, within a defined set of rules, many material elements can change without altering the overall functioning of the system. In other words, the system may evolve relatively easily, which is an important feature of biological systems [10]. Along these lines, I proposed earlier that the ultimate definition of self/non-self discrimination in adaptive immunity lies within the set of rules that define the avidity of interactions between lymphocytes. This may hold for innate immunity as well, since self molecules are discriminated from non-self by affinity thresholds. Then, it appears that, contrary to the initial formulation, MHC molecules, which shape the identity of individual immune systems, have no role in determining the self. On the contrary, the existence of virtual rules, common to all individuals, is what permits the free evolution of MHC molecules, and, therefore, tolerates their remarkable polymorphism [11].

In this context, the notion of robustness in immunology deserves more attention. Robustness is a distributed property, known to occupy a large space in human artefacts, as it probably does in biological systems (a "minimal" bacterium may work with less than 1000 genes, while *E. coli* has more than 4000). Robustness often translates into quality control mechanisms that check upon critical processes. The immune system has many such quality control mechanisms, as shown, for example, by the multiplicity of controls that check upon the activation of naïve B and T cells. Actually, the very existence of B and T cells, that is, the existence of a double recognition system of the antigen, appears an essential quality control device, as strongly suggested by its occurrence in lampreys [12]. Autoimmune pathologies may then find their source either in primary deficits or in secondary defects in the quality control devices that supervise the primary mechanisms [11]. This way of thinking may be stimulating, but it faces the aforementioned difficulty of defining quality control mechanisms as identifiable modules. It also calls attention to the identification of fragile points in immune networks.

The immune system has a multilayered architecture, but cannot be seen simply as a set of Russian dolls (molecular, cellular, multicellular, etc.) fitting into one another, because the layers interact in many ways. Robustness and fragility have to be considered in the interactions between layers as well as in each of the layers. Indeed, failures in the interactions between layers are likely to make the system catastrophically collapse. Doyle and Csete [13] made the interesting point that, rupture innovations being rare, the fundamental driving force in the evolution of biological systems is likely to be the improvement of robustness rather than minimal functionality.

Along similar lines, I recently proposed a hypothesis to complement current evolution theories with the notion of "selfish cellular networks" [14]. In complex organisms such as humans, gametogenesis takes many cellular generations (more than 200 for human spermatozoa), creating a space for mutational experimentation and selection

within the body. Rates of mutation are such that, statistically, all gametes ultimately bear multiple mutations. My hypothesis proposes that, because of the robustness and autonomy of "selfish" cellular networks, the latter are checked upon as groups rather than as individual mutations. A selective process acting at defined check points would primarily result in the surveillance of domestic functions. It would allow their evolution and possibly lead to increases in this robustness. Precisely how this would apply to the immune system is speculative at this stage, but it should be noted that cells involved in spermatogenesis are not immune to infection.

To sum up, complexity is bound to become an essential part of research in immunology. With the help of new technologies, systematic immunology provides an overwhelming amount of data, which systems immunology is currently unable to use. A major challenge is to reverse this situation.

On the future of the applications of immunology

Promises

In life sciences, the distinction between basic and applied research is less pronounced than in other fields, partly because biology is unified by evolution. Thus, it is widely accepted that findings in bacteria, flies and other organisms all help in understanding humans. Immunologists have claimed for decades that their science will have a major medical impact. Many have overemphasized the applications of their work, either by excessive enthusiasm and underestimation of the downstream constraints of translation to humans or by the sociologically understandable concern of achieving recognition (and funding). For example, vaccines marketed today have mainly been developed on empirical grounds, with relatively little input from immunology—except for the concept of conjugated vaccines, which is truly immunological. Nonetheless, the field of diagnostics has made enormous progress thanks to monoclonal antibodies. Numerous therapeutic monoclonal antibodies are also licensed, and many more are being developed. Cellular immunotherapies are coming up, and rational vaccine design is on the horizon. Therefore, the future realistically does appear promising.

My own view is that the medical importance of immunology can only increase. One reason is that inflammation is now known to play a major role in a growing number of pathologies (including, for instance, diabetes type I and II, and obesity). In addition, the IS interfaces with other systems in the organism, and provides systemic relays. This is the case for the endocrine and nervous systems, as well as for the gut microbiome, which receives more and more research attention.

In parallel, the importance of systemic approaches will also grow. After all, each finding of unexpected toxicity in drug development reflects insufficient systemic knowledge. It now makes sense to modelize individuals in virtual clinical trials as a preliminary step in the design of more focussed trials. At the same time, immunology is a strong component of personalized and stratified medicine. The IS of each individual has an identity strongly shaped by its MHC as well as by other genetic and epigenetic factors, some associated with ethnic characteristics, which are becoming better and better documented.

Limiting factors

To assess the value of these promises, it is useful to examine the technical and non-technical limiting factors. I rely here on my past experience in vaccines, as well as on work currently being performed at the Singapore Immunology Network (SIgN), a research centre founded towards the end of 2007. SIgN's aims are devoted to human immunology, so that its activities are closely associated with medical translation. Some of the following considerations make use of recent experience gained in this context.

Biological engineering Biological engineering per se (not the knowledge underlying it) appears less and less as an obstacle to progress, and increasingly as a facilitator. For example, human monoclonal antibodies can now be produced at high throughput, making the process of "humanization" of mouse antibodies unnecessary and obsolete. Engineering aims to improve bio-availability and effecter activities of the constructed molecules. Bi-specific antibodies may have strong potential. This assessment is supported by the observation that, due to hetero-ligation, certain antibodies generated in vivo are functionally bi-specific. Monoclonal antibodies constitute a rather homogeneous class of pharmaceutical molecules, which facilitates their development. Considerable knowledge has now been accumulated in the field. On the diagnostics side, monoclonal antibodies might be complemented by aptamers. Progress in microfluidics contributes to reduce volumes, time of operation and cost, while increasing multiplexing.

The key role of immuno-monitoring The development of new drugs and vaccines for humans depends to a large extent upon our analytical capabilities. Measuring a vast number of immune parameters in blood samples or biopsies is essential for research as well as for development. Importantly, the correlates of the immune control of many pathogens in humans are still unknown. This is one of the reasons why vaccine trials remain empirical and may require the recruitment of up to 100,000 volunteers. In addition, the primary and secondary effects of new drugs

need to be evaluated, for efficacy and/or safety reasons. For example, given the growing evidence for the importance of inflammation in a range of conditions and pathologies, it is not unreasonable to check the immunological impact of a new antibiotic. Finally, immuno-monitoring is also critical for the development of personalized medicine across many disease areas.

However, extensive immuno-monitoring carries with it a number of constraints, well indentified in SIgN by John Conolly's group [15]. The most obvious ones pertain to the multiplicity of measurements and, therefore, their cost; hence, the need for high throughput, automation, cost optimization, etc. But it is also necessary to employ standard operating procedures in order to acquire and store information in such a way that data originating from different sources can be integrated when needed. Ideally, this should hold over time; for example, data acquired with an improved instrument should somehow be comparable to those previously collected before the advent of the new technology. The system must also include the data contributed by clinicians. Altogether, large scale immuno-monitoring is itself a complex system.

Clinical experimentation The most important limiting factor turns out to be clinical experimentation. A phase I clinical research trial run in western countries often costs several million Euros and takes 2–3 years. This is hardly affordable by most academic institutions. In addition, academic researchers involved in such efforts face the deficit of recognition associated with the lower publication rate inherent to this type of activity. The availability of patients and volunteers is becoming another problem. Not taking into account the much higher costs associated with phase II and phase III trials, usually taken up by industry, the situation is such that only a small proportion of potentially useful treatments reaches the clinics. Selection criteria often fall short of scientific evidence, leaving room for non-scientific, sometimes even political, arguments to prevail.

The criterion of market size in the industry and the race for blockbusters also creates a strong bias. This holds true for most areas of drug development, but particularly applies to immunology because animal models are of limited value. The mouse is beautiful for immunological discovery, but is not a good predictor of immune reactions in humans. Thus, the larger number of vaccines and adjuvants that work extremely well in the mouse have failed in clinical trials. Therefore, the rhetoric of the "Golden Age of Vaccines" may reflect more the availability of additional funding (e.g. by the Gates Foundation) than the actual state of the science, emphasizing the need to focus more on human immunology and on extensive immuno-monitoring, as we decided to do in SIgN [15].

The social conditions of the evolution of research and its applications

The above remarks call attention to a number of social conditions, which frame the current trends and future of research and its applications, in biology at large and immunology in particular.

The necessity of mutualizing and sharing knowledge

Mutualizing and the sharing of knowledge have become compulsory features in several domains of science, such as astronomy, physics (e.g. CERN) and climatology on the global scale. Life sciences have started doing so, as illustrated in the 1990s by the international distribution of tasks to determine the first complete yeast and human genome sequences. This trend should be strengthened with the study of complex systems. Systematic biology (including immunology) generates huge amounts of data that need to be shared for science to make efficient progress. As in other domains, transnational agreements and organizations are required in order to: (a) agree on the formats in which data are acquired and stored and (b) determine the rules of sharing. This is very challenging in life sciences. For example, today, transcriptome data obtained in different laboratories are often not quite comparable, resulting in a considerable loss of scientific effort and money, not to mention the loss of potential breakthroughs that may go unnoticed.

Sharing the benefits of knowledge

Sharing the benefits of knowledge is another major and complicated problem, which spreads across several sectors of our society. It involves individual researchers and their teams, their institutions, the national and international funding bodies, as well as the private sector, which develops the knowledge into marketable products. This raises numerous issues on patents, license agreements, etc., which I shall not review here.

One would expect the benefits of knowledge to be shared in a fair and equitable fashion. This issue is particularly acute when it involves essential goods such as vital vaccines and drugs. Take the anti-retroviral drugs against HIV; billions of dollars of public and private funds have been gathered worldwide to provide these medicines to about half of the infected people, for free or at a very low price. This remarkable success, however, has its limitations. The Doha agreements have modified patent policies to permit local manufacturing with only limited impact. Not all patients are covered, and the funding remains fragile, especially after the 2008 financial crisis. What about other infectious diseases? It is worth recalling that,

until 12 years ago, about 800,000 children died every year from measles and its complications, while a safe, robust and efficacious vaccine was available for a few cents. This figure has dropped to 200,000 in 2011, largely thanks to the GAVI organization.

This issue goes beyond infectious diseases. Some of the latest anti-cancer treatments are very expensive, up to 100,000 euros per patient per year. They are obviously unaffordable in poor countries. Is it more equitable to die from cancer than from AIDS through lack of resources? This argues for a more general policy of differentiated prices for essential drugs [16], as practised for several decades for essential vaccines and today for treatments against HIV.

The increase in the cost of medical innovation

The above example of cancer drugs applies more generally and illustrates the general problem of increase in the cost of medical innovation. It now takes about 1–3 billion euros to develop a new molecule or a new vaccine, a figure which has more than doubled in 15–20 years (this is an estimate because there are few well-documented and reliable studies on the issue). In addition, while biological research has made enormous progress in the last decades, the number of entirely new products that have reached the market has dropped by almost a factor of two over the same time. This paradoxical phenomenon has serious consequences for the structure of the pharmaceutical sector. The narrowed drug and vaccine pipeline implies that many potential products are dropped in the course of development. Since new products are increasingly expensive, social security systems have trouble keeping up; needless to say, this is a disaster for neglected diseases, that is, the diseases that are specific to poor populations in the world for which no efficient drugs are currently available. They include many tropical diseases such as malaria, Chagas disease, leptospirosis, schistosomiasis and several others. New drugs are urgently needed, but how could industry spend billions on research and development for people who cannot pay for the drugs? It must be emphasized that research is not so much the issue because many academic institutions have research programs dealing with these diseases. The point is that there are not enough resources worldwide for development, including clinical trials, formulation, etc. Therefore, the vast majority of research findings are bound to remain unused, if not useless.

This rise in the cost of innovation is a very serious issue. Even in rich countries, innovation in drugs and vaccines may soon become unsustainable. I shall not analyse here the chain of transfers between academia, biotech companies and large pharmaceutical firms. I will instead focus on one point, namely the social cost of precaution.

Having been involved in a thorough analysis of the so-called "precautionary principle" [17], I have since reflected in depth upon its impact in drug and vaccine development, and reached three conclusions [18]. One is that the precautionary attitude (if not the explicit precautionary principle), as relayed by the international regulatory agencies (mostly the FDA and EMA) is probably responsible for a significant share of the rise in the cost of medical innovation. Another is that the direct and indirect costs of regulations, as well as their impact, are usually poorly documented. Some are probably useless and/or unduly expensive. Hence, a plea in favour of "Evidence-Based Regulation", a discipline that could follow the path set by "Evidence-Based Medicine". It is recognized today that the latter has considerably helped in rationalizing medical practise and costs. Finally, there are serious ethical issues in exporting the precautionary principle, together with its associated costs, to developing countries that cannot afford them—especially when this is promoted under the banner of a universal moral. Interestingly, the regulatory fortresses, which were built to be independent and impregnable, have started being shaken by China, which has simply decided not to comply with some of their rules. The Chinese rationale is approximately that used in the past by patients' associations in the USA, namely that people do not have to die because the availability of new drugs that could save their lives is delayed for unjustified regulatory reasons.

Demography and evolution of the society of researchers

Let us now consider the evolution of the society of researchers, starting with the following observation: research demography is changing considerably. In France, the number of researchers in life sciences has grown from a few thousand 50 years ago to 60,000 or more today, amounting to about 0.1 % of the total population. The time of the Cold Spring Harbour "phage club", in which I was lucky enough to participate, at the end of the 1960s, is over. Nowadays, there may be more than one million researchers in biology in the so-called developed countries alone.

My point is that, in perhaps 10 or 15 years time, this number will have doubled with the growth of the research sector in Brazil, China, India and other emergent or emerging countries. What will happen then? Regarding immunology, it seems to me that the same results are often published as much as 5–10 times, reflecting a major defect in originality. Is this redundancy index (which warrants careful definition and measurement) going to double with the doubling of researchers? In publicly funded research, would this be acceptable to the taxpayer? At the very least, I consider it urgent to more carefully assess the social externalities of research, especially in terms of education and medical advancement, and not only in terms of direct economic benefits.

The alternative is the diversification of research topics. Would it involve an evolution of goals and aims and the emergence of new research sectors? With a growing drive for personalized medicine, should research be more focused on innovative services? Should biological research ally more closely with humanities to promote social innovations?

Another issue relates to the increase in the number of scientific publications. Scientific information is more and more difficult to master. Oral information is making a comeback, and the influence of informal communication networks is growing. The publication system has drifted. Peer review is often deficient. The so-called prestigious journals are too pre-eminent: impact factors and quotation indexes are overused and occasionally manipulated. Young people are not equitably treated when such indicators are utilized, without discrimination, to decide their careers. Here and there, excessive pressure based upon the same indicators results in many small, and a few much bigger, frauds.

What else could we do? A prerequisite for scientists is to recognize that the conditions of research practise have profoundly changed, and will further change considerably. In my view, the democracy of researchers should devote more time and effort to reflect on its own social structure and upon some desirable improvements. Among these, there is a need to raise the moral standards in various areas of the research field, including peer review, publications, conflicts of interest, independent expertise and so on.

I contend that science is so far the most beautiful example of democracy in human societies. Scientists generate knowledge rigorously, validate their results, share them, discuss them and usually come to agreements. Scientific tribes do not vote to decide upon what is right or not. They discuss and try to agree. In my view, scientists do not care enough about their own democracy. They do not fully realize how exemplary it is and should continue to be. Furthermore, they do no fully realize that science can, and must, contribute to public debate and action, not only by providing data and results, but also by promoting its method. In this sense, I strongly believe that new types of science may and should arise. I discussed above the need for a science of regulatory affairs, which I termed Evidence-Based Regulation [18]. In another context, I think that it is possible and desirable to generate a science of action in fighting against poverty [19, 20].

What should we teach our students? This may be the most important immediate question. In immunology, I suggest a few important lines of discussion: how to deal with complexity; how to accommodate techniques and concepts, and local and systemic issues; to what extent knowledge has to be mutualized; how to manage the relationships between science and the world of finance and industry; and how to equitably share the benefits of research.

Ladies and gentlemen,

It is now time for me to conclude and close this year's cycle of conferences, as well as 12 years of teaching in this wonderful and remarkable institution—The College de France—that has stood for almost 500 years. At this moment, a quote taken from the French Poet Stephane Mallarmé comes to mind:

"Man, then his authentic sojourn on Earth, exchange a wealth of reciprocal proofs."

"L'Homme, puis son authentique séjour terrestre, échangent une réciprocité de preuves."

What I wish to emphasize is that our "authentic sojourn on Earth" is itself a matter of chance and specificity. For me, the chance has been to have benefited, and still benefit, from an exceptional family environment, and to have been associated with great people, such as my initial mentor, François Gros. I have also had, and still have, the chance to have superb collaborators, without whom I would be nothing or very little. What are my specificities? There is one that I want to explain: it is the choice that I have consistently made to carry out both basic and applied research, and to participate both in the acquisition and utilization of new knowledge. Maybe my science and my teaching would have been more profound if I had not developed the second part; but this was my choice. I have always believed that science should **serve**, in the two meanings of this term: be useful and be at the service of the others. These are the goals I have pursued and will go on pursuing.

Thank you for your attention.

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