

# Basic Sciences Fertilizing Clinical Microbiology and Infection Management

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Basic sciences constitute the most abundant sources of creativity and innovation, as they are based on the passion of knowing. Basic knowledge, in close and fertile contact with medical and public health needs, produces distinct advancements in applied sciences. Basic sciences play the role of stem cells, providing material and semantics to construct differentiated tissues and organisms and enabling specialized functions and applications. However, eventually processes of “practice deconstruction” might reveal basic questions, as in de-differentiation of tissue cells. Basic sciences, microbiology, infectious diseases, and public health constitute an epistemological gradient that should also be an investigational continuum. The coexistence of all these interests and their cross-fertilization should be favored by interdisciplinary, integrative research organizations working simultaneously in the analytical and synthetic dimensions of scientific knowledge.

**Keywords.** basic sciences; microbiology; infection; innovation; experimental organizations.

Microorganisms constitute the simpler expression of cellular life, and therefore any new knowledge about microorganisms is a contribution to the understanding of life in general. Microbiology is therefore not only the science of microbes, but micro-biology—biology of the fundamental biological entities. But some microbes (a huge minority) are also causing infectious diseases, and many others (a huge majority) influence individual, public, and environmental health. Therefore, microbiology constitutes a crossroads where fundamental biology and health interests necessarily converge.

Slightly more than 150 years ago, on 7 April 1864, Louis Pasteur presented in one of the “Soirées Scientifiques de la Sorbonne” [1] his seminal conclusions about a fundamental (maybe the more fundamental) topic of biology, spontaneous generation: “The spontaneous generation of microscopic beings is a mere chimera ...” This is a founder statement of basic science, as what is true for a microbial cell is true for all type of cells and forms of life. But Pasteur was fully conscious that microbes were not only experimental objects to understand life in general, but *agents* to explain the constant transformation of the Earth:

“This is the role of those tiny beings which serve as agents of fermentation, putrefaction, and disorganization of everything on the surface of this globe ... this role is immense, marvelous, positively moving” and—much more widely known—causative agents of infectious diseases.

## DISCOVERY, THE DEEP TASK OF SCIENCE

The term “science” derives from very old Indo-European roots (the Indo-European *skei*; *skhizo* in the Greek, and *scindo* or *scindere* in Latin derivatives), meaning to split or to cleave something with a knife. The sense is to reveal what is hidden below the surface, below the external appearance, to remove what is covering the reality, to discover. It is not by chance that the origin of modern medical sciences in the Renaissance times is tightly linked to anatomical dissection, the scalpel serving as an early scientific tool facilitating discoveries inside human bodies. Indeed, the first scalpel of microbiology was the microscope, but many other technologies of physical, chemical, and, more recently, of computational nature have allowed along the last 2 centuries to go deeper in the discovery of microbes. Note that frequently these tools used in microbiology or infectious diseases are imported from other areas of scientific knowledge, and a critical part of the success in scientific discovery is depending on the creative importation and application of novel tools to use them as updated scalpels. But it should be stressed that to “discover” is primarily unlinked with any applied activity; only the structure and function of the microbiological matter is revealed. Only in a second step, such findings might be used to imagine ways to influence the biological behavior, giving rise to secondary or applied sciences.

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## **BASIC SCIENCES AND INNOVATION: TRIGGERING FORCES AND OBSTACLES**

Basic sciences are those which are devoted to fundamental theoretical or experimental investigative research to advance knowledge without a specifically envisaged or immediately practical application, in the quest for new knowledge and the exploration of the unknown [2]. Thus, the main epistemological force triggering basic sciences is the curiosity, immediately followed by creativity, to find the way to enter and explore the unknown spaces [3]. Because of that, progress occurs more rapidly when investigators are allowed to pursue their passions [4]. In a certain sense, basic sciences only look forward, ignoring the consequences of the new elements of knowledge. Basic sciences play the role of stem cells providing material and semantics to develop functional (applied) tissues and organisms. Differentiated tissues are certainly much less creative (innovative), but this Lamarckian view can be mitigated by the occasional possibility of de-differentiation of specialized into stem-like cellular entities. An intelligent deconstruction of applied themes might also reveal unanswered basic questions (reverse translational research).

Of course, the net result of basic science is knowledge innovation. Basic science is a bedrock of progress [4], but the current dominance (not only in the industry, but also in public agencies, and even in academic research institutes) of clerical “science managers” orientates research to rapid obtention of funds, patents, and rapid return of investments. The success of science is frequently oriented as gaining success for management, which orientates the otherwise naive scientists to take the right path of societal progress (frequently disguised as public health needs or interests), just measured in the framework of monetary units. As it was stated by Francis S. Collins, “when everybody gets to one side of the boat, it usually tips over”—meaning that if all investments are located on one part of the research continuum, the business-oriented research, the entire enterprise of discovery, innovation, and progress may sink [5].

In fact the requirements of the clerical “management of science” evaluation, funding, and communication structures rarely selects creativity and innovation, and certainly fosters vulgarity and sterile repetitiveness in science. Repetitiveness provides a certain flavor of truth, so that any creative novelty is taken as suspicious of scientific weakness. The result is a rampant plethora of journals publishing avalanches of manuscripts, with the consequence of an “inflation” in the intrinsic value of knowledge; eventually important findings might remain buried forever among tons of irrelevant reports. An important secondary effect of this inflationary process is the perception that almost everything has been already published, and that the only possibility of contributing is at the expense of minor variations of what is already known, reducing the creative excitement of passion associated with creativity and creativity recognition and condemning the scientist to an increasingly clerical type

of work. The increasing fashionable trend of network research, which is certainly of interest in applied sciences, certainly does not contribute equivalently to creative discovery, which is more based on individuals than groups.

## **BASIC SCIENCES LAYING THE FOUNDATIONS OF CLINICAL MICROBIOLOGY AND INFECTION MANAGEMENT**

An operative-descriptive definition of basic sciences fundamental research in clinical microbiology and infection management is proposed here. These sciences are devoted to the understanding of unknown mechanisms and processes involved in cellular physiology (cell biology, biophysics, biochemistry), genetics (vertical and horizontal transmission of genes, and the rising of phenotypes), cellular adaptive biology (variation and selection), microbial multilevel population biology (from genes to mobile genetic elements, clones, and microbiotas), interactions biology (as host–bacterial interactions, including those of entomological bases; immunobiology, immunogenetics, and microbiota biology), pharmacodynamics (drug–microbe interactions), ecobiology (microbe–environment interactions, including transmission biology and basic epidemiology), and evolutionary biology (microbial variation and selection along time, evolutionary trajectories). These basic sciences constitute the source of translational research, “the process of applying ideas, insights and discoveries generated through basic scientific inquiry to the treatment or prevention of human (infectious, in our case) disease” as defined by the National Institutes of Health (NIH) [6].

Note that the process of scientific knowledge “lost on translation” [7, 8]—that is, unsuccessful translation of basic insights into medical practice—has somewhat discredited in recent years the role of fundamental sciences. As in professional language translation technologies, the efficiency of translation depends mainly on the current scarcity of good “translators” (understanding both basic and practical languages) combined with the number and complexity of languages in the increasingly diversified field of sciences. The NIH-based National Centre for Advancing Translational Sciences initiative (<https://ncats.nih.gov/>) is a promising organizational tool [9], but as Fang and Casadevall stated, “history has taught us that the path from basic discoveries to scientific and technological applications is seldom a straight line” [8]. In other words, we should consider that there is no dictionary providing translation of a “basic” word to an “applied” word; in fact each word-to-word translation is the result of a scientific inquiry by itself. Note that understanding a translation requires the recognition (even in an obscure way) of something common between the “basic” and “applied” expression, and that occurs probably across a trial-and-error process. Future advances in knowledge engineering and semantics, eventually combined with educational programs [10, 11], might facilitate such complex tasks. But an essential message is that the existence of a bottleneck (the translation)

should not impede the development of basic sciences, as basic “words” will be able to find by themselves a way of being translated into applied meanings, also in microbiology and infectious diseases. These opportunities for translational activity might paradoxically be more fruitful in nonprofit groups, where scientists have the real scientific freedom required for discovery, where individual volunteering or interning experience are vital to meet innovative approaches [12]. In fact no systematic relationship between the “basic” versus “applied” research focus of a grant and its propensity to be cited by a patent has been found in recent studies [13].

### **CLINICAL INFECTIOUS DISEASES: FROM PRACTICE TO SCIENCE**

The behavior of clinicians is frequently based on practice, but this practice is not always rooted in solid science. Of course, diagnostic algorithms or therapeutic protocols are based on the analysis of collections of observations. But on too many occasions the results of a relatively short number of cases along clinical trials are converted into an “established knowledge” that is difficult to modify in the future. When this knowledge is turned into frequent practice, emerge in the guidelines, or reach the medicine schools and hospital residency training programs, science has not much more to say.

Common sense might suggest that we need a consistent way of turning practice into science. Consider, for instance, the millions of patients suffering bacterial infectious diseases that are treated with antibiotics; in hundreds of thousands of them, we know the offending organism and its susceptibility to antimicrobial agents. Now, try to find in the medical literature how the *in vitro* level of susceptibility correlates with the degree of clinical success. You will generally find little more than the data (many of them historical) during clinical trials, which are carried out on limited populations of patients that do not represent the richness in diversity of patients in real-world medical scenarios. And that will correspond only to a few particular dosages of the drug, based on limited preliminary pharmacokinetic/pharmacodynamic data; in turn, these data are based on minimum inhibitory concentrations, which frequently are the only pharmacokinetic parameter used, disregarding such critical factors as the biology (ecobiology) of cells in the site of infection, or the role of innate immunity. How will the drug behave in different type of infections caused by a given organism? Which type of response can be expected from different types of patients of different ages, normal or impaired immune response, with different underlying diseases, or with different concomitant therapies? In fact, after almost a century since the start of chemotherapy, we are unable to know in a quantitative way the risks and benefits of the use of antimicrobial agents [14]. And regarding clinical responses, why can we not “put numbers” in the different degrees of clinical response, developing solid clinimetrics procedures? All these are legitimate questions

that remain without a scientific answer, just because they are depending on an extremely large number of observations.

### **BASIC SCIENTIFIC METHODS FOR CLINICAL SCIENCES**

Science is frequently based on comprehensive collections of relevant data and observations. It is critical not to lose the great deal of information contained in usual medical practices. The observations required for doing science that were mentioned in the last paragraph are frequently available, but we have disregarded the tools and methodology of capturing and analyzing them in a precise, cumulative, continuous (online) way. However, we really need these data to root our practice in scientific data. For instance, if clinicians in a particular place were made aware online of the frequencies of resistance to a particular antibiotic, and prescribe accordingly with this updated knowledge, mathematical models predict that bacterial resistance will not continue to increase, but rather will be leveling off, reaching, and maintaining a stable internal equilibrium [15].

Beyond these examples concerning antibiotic therapy, much more precise information is critical to shape appropriate interventions in many other areas of infectious diseases management, including the effects of diagnosis, therapy, and hospital infection control. Hospitals are continuously running, and events constantly occur that are neither detected nor systematically recorded, preventing also here reaching an organized ensemble of significant data. Certainly a cohorting policy needs to be put in place both in hospitals and the community to create homogeneous cumulative ensembles of patients making possible studies to reach scientific conclusions. These will eventually serve to develop targeted interventions, but also innovative products, processes, or services—new solutions to be developed by ad hoc start-ups.

### **BASIC SCIENCES AS EDUCATION FOR OBJECTIVITY**

Medical practice is frequently flawed with “empirical” and “traditional” considerations, not always well proved. Indeed, both clinical and basic sciences might have the temptations of apophenia (when we believe in our detection of patterns in random data), confirmation bias (when we focus our attention toward the data confirming our expectations) [16], and hindsight bias (when we tend to see an event as predictable only after it has happened), therefore reducing the reproducibility, the efficiency, and consequently the credibility of science [17]. We advocated in former paragraphs in favor of the “passion of knowing” as a source of innovative thinking and creativity, as a condition for the progress in science. But passionate researchers should be aware (more than any other) of the temptations of passion, as false assumptions might result in false trajectories in science, extremely difficult to correct once installed in practice. Basic scientists are frequently more aware of the constant need

of appropriate controls, and generally have accessible tools to observe from different perspectives of a single event. Certainly basic sciences have a heuristic potential for the training of medical sciences.

## EXPERIMENTAL ORGANIZATION OF BASIC-APPLIED SCIENCE TRANSITION AND MANAGEMENT IN MICROBIOLOGY AND INFECTIOUS DISEASES

Among the key tools assuring the progress of the transition between basic and applied sciences, we should highlight scientific organizations. Scientific organizations are themselves the object of science—that is, innovative organizational hypotheses should be constructed and tested for efficient behavior in progressing toward novel and significant knowledge [18]. The interest of putting together in the same hospital organization basic and clinical microbiology with infectious diseases, but maintaining its own specificities, was proposed and successfully tested decades ago [19, 20]. The university hospital-based Méditerranée Infection Foundation in La Timone, Marseille (France) is an example of such experimental organization, ambitiously merging discovery-driven basic microbiology with research in novel analytical tools, experimental pathogenesis research, diagnostic, clinical, therapeutic, preventive procedures (encompassing the individual, hospital, and community), and epidemiology-ecology, facing the urgent challenge of public health microbiology and public health infectious diseases perspectives [21, 22], and, in general, global health. Global health in fact is a transnational, interdisciplinary effort synthesizing population-based prevention with individual-level clinical care [23]. This organization aims to act also as a knowledge center, fostering cognitive capability, skills, training, and learning in novice scientists including from less developed countries, and intending to promote skilled scientists at both sides of the necessary exchange bridge between basic and applied sciences. In this particular organization, the fact that this advanced research institute, Méditerranée Infection, is placed in proximity to a school of medicine offers an opportunity for approaching basic science to clinicians. As William Osler said at the opening ceremony of the Wistar Institute for Anatomy and Biology in Philadelphia, 21 May 1894, “Particularly for a medical doctor, to be learned in a scientific discipline is an essential gift that ferments all his life.” That is exactly what we need for the progress of medical sciences, and in particular for the progress of microbiology and infectious diseases.

## Notes

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