PREFACE: ON PARADOXES AND PROGRESS IN SCIENCE

What is a paradox? In the present scientific context, the word paradox has a widespread usage that can be simply and precisely formulated. A scientific paradox exists when there is a conflict between some well-supported and widely accepted theoretical dogma or framework, and some piece of observational or experimental data. The piece of data is then a paradox within that particular theoretical framework.

Paradoxes play a pivotal role in the advancement of science. Many major breakthroughs in science were preceded by the emergence of one or more paradoxes within the prevailing theoretical framework. In each case this was the prelude to what Kuhn has called a "paradigm shift". Perhaps the most dramatic examples of the key roles played by paradoxes are in physics. Two of the greatest intellectual achievements of the 20th century, namely quantum theory and relativity, were spawned by paradoxes.

Quantum theory in its earliest form was born as a response to a paradox known as the "ultraviolet catastrophe". Calculations were made by Raleigh and Jeans, in the framework of the elegant theoretical edifice of classical physics, of the intensity of radiation from a black body as a function of temperature and wavelength. The theory led to an equation which predicted that the intensity goes to infinity as the wavelength is decreased to zero. The experimental results agreed with the Raleigh-Jeans equation at long wavelengths, but at the short wavelength (ultraviolet) end of the spectrum the intensity fell to zero. The predictions of classical physics were unambiguous, and the experimental result was also unambiguous, but the two were irreconcilable — hence the "castastrophe". Max Planck resolved the problem in a highly remarkable fashion. He first sought a way of modifying the Raleigh-Jeans equation such that it would yield agreement with the experimentally observed spectrum. He then proceeded to search for a physical interpretation of the new equation. Planck's quest led to the first form of quantum physics. The only interpretation he could find for the new equation was that the radiated electromagnetic energy occurred only in integral multiples of $h\nu$, where ν was the frequency, and h was a very small quantity that became known as "Planck's Constant". This was the beginning of Quantum Theory, which quickly developed into a cornerstone of 20th century physics, and which bears a similar relationship to physics and chemistry as molecular genetics does to biology.

The paradox that helped pave the way to Einstein's Theory of Special Relativity resulted from the famous Michelson-Morley experiment. Michelson and Morley attempted to measure the velocity of the earth relative to the ether, a medium that was assumed by 19th century physicists to be necessary for the propagation of light waves. The highly precise interferometer which they constructed for this purpose was capable of detecting effects one tenth as big as the theoretically predicted effect, but no evidence of the expected relative velocity could be seen. This paradox within the classical physics theoretical framework was resolved when Einstein showed that a self-consistent theory (Special Relativity) could be based on the premise that the velocity of light is the same for all inertial observers.

It is less common to portray important advances in biology as being due to the formulation and then the resolution of paradoxes. A careful reading of the historical record suggests however that the greatest single advance in theoretical biology, the formulation of the theory of evolution by Charles Darwin, emerged from a paradox. There was a sharp conflict between Darwin's observations and the orthodox theoretical framework which he had when he embarked on his "Beagle" voyage. Darwin had accepted without question the fixity of species and their special creation as depicted in Genesis when he started out on his historic journey. During the ship's visit to the Galapagos Archipelago in 1835, he observed that there were very small differences between the so-called species inhabiting different islands. This observation was a paradox within the prevailing theoretical framework of the fixity of species, and he very soon realized that the paradox could be resolved by the idea that species gradually become modified. The theory of evolution that he subsequently developed revolutionized both science and philosophy, as no theory before or after has done.

We do not suggest that the theoretical advances that will come from resolving the paradoxes in this book will compare with the breakthroughs of Planck, Einstein, and Darwin. We do, however, suggest that the mechanism of progress in our theoretical understanding of nature is the same, whether we are concerned with the very dramatic advances like those described above, or with less imposing, but nevertheless fundamentally important smaller steps in the forward march of our understanding. In either case we believe it is incumbent on scientists to focus attention on what they do not understand, rather than to spend too much time basking in the satisfaction of what is understood.

Not all paradoxes lead directly to new insights, of course; on the contrary, they can also lead us away from the truth. An example can be seen in the history of evolutionary theory. Six years after the publication of Darwin's *Origin of Species,* William Thompson (Lord Kelvin) described a paradox that existed within the combined framework of (1) Darwin's postulate that the earth is many millions of years old, and (2) the physics of the time. Thompson calculated that following solidification, the earth would cool rapidly (on a geological time scale) to temperatures lower than those now prevailing, and that the many millions of years required in Darwin's theory for evolution were not available. This paradox was compelling from the point of view of a 19th century physicist. Physics was regarded (at least by physicists) as a soundly based empirical science, in contrast to the seemingly wild speculations of a biologist about what might have happened in the course of millions of years in the past. Many physicists were therefore convinced via Thompson's paradox that the theory of evolution was untenable. If all the biologists of the day had been physicists, Darwin's theory might have received short shrift. The resolution of the Thompson paradox came later with the discovery that the physics side of the story was incomplete. Radioactivity was discovered at the turn of the century, and it was deduced that the natural radioactivity of rocks is a source of heat. This radically changed the calculations, so that the physical data became compatible with the many millions of years required by the theory of evolution.

The moral of the preceding example is that we cannot tell from the existence of a paradox which part of our thinking is wrong. One can easily jump to the wrong conclusion. The usual response to a paradox is to conclude that the theory is wrong; frequently however, the theory is not wrong, and the data are being wrongly interpreted. In any case, the formal delineation of the paradox serves to highlight the existence of a problem that deserves study, and which might reward such study with fundamental new insights.

Our strategy in assembling this volume was quite simple. We wrote to 150 immunologists, asking them whether they would like to contribute a chapter to an anthology of paradoxes in immunology. Forty of them declared their willingness to do so. When it came to the crunch, that willingness translated into 27 actual manuscripts.

The slightly lengthy letter of invitation included the following paragraphs:

> In our view, paradoxes play a key role in the advancement of science. They are associated with excitement, and with the knowledge that we must be looking at something the wrong way. The clear formulation of a paradox can herald important advances, since the resolution of the paradox is generally a conceptual step forward. It is therefore of paramount importance to identify paradoxes and focus attention on them.
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> Some fields of science do not have any paradoxes (for instance chemistry?), and they are fields that are essentially solved and consequently boring. On the other hand there are many paradoxes in immunology,

but they are often almost lost in the mass of descriptive, less exciting immunological literature. We hope that by assembling a succinctly formulated collection of paradoxes, old and new, the rate of progress in immunology can be enhanced.

Paradoxes come in many shapes and sizes. Some are widely known, some known only to a narrow circle of specialists, and many are known only to an individual investigator who didn't publish a finding because he or she could not make any sense out of it. Some are old and half forgotten but unresolved; some are new and not yet well publicized. Some concern your own data; some you know from the literature. We would like to include all types in our collection. This could, for instance, be a chance to publish that old observation that didn't seem to make any sense, and which you therefore never wrote up.
We suggest the following format for all contributions:

1. Theoretical Framework — A description of the theoretical framework (dogma) within which the observation is paradoxical. This is important, since an observation that is paradoxical within one theoretical framework may not be in another. The framework described will be generally accepted or widely influential dogma, or else some strong justification for it should be provided.
2. The Observation — This section can refer to published data, or may consist of previously unpublished data. It may be your own, or refer to work by others.
3. Discussion — Discuss the paradox as you see fit. Please note that if a completely satisfactory resolution of the paradox is provided, it is no longer a paradox, and we do not want it in the collection.

We suggest that after preparing your manuscript, you nominate three immunologists with expertise in the area of your paradox, and we will forward copies of your manuscript to them, asking for comments (to be published). You will be given the chance to respond to the comments. This will provide the reader with a view of the same phenomena from different perspectives. It should also help to give him (her) a sense of which phenomena are widely regarded as paradoxical, in contrast to cases of a paradox existing only within a less widely accepted theoretical framework.

We believe that the importance of the contributions made by the commentators cannot be overemphasized. Theirs was often an extremely difficult task, perhaps more difficult in some cases than the task of writing the actual chapters. In this respect, paradoxes in immunology seem to be like problems in the discipline of philosophy. In philosophy, the publishing of a commentary on a paper is conventionally considered to be worthy of about as much credit as the publishing of a paper. We feel that such a convention should be adopted also for the commentaries on paradoxes in immunology.

Should more volumes of *Paradoxes in Immunology* be produced? We believe that this collection of paradoxes only scratches the surface of the unresolved conundrums in a vast and complex field. If you would like to contribute a chapter to another volume of paradoxes, or if you would like to suggest a topic for a chapter, please write to us.

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