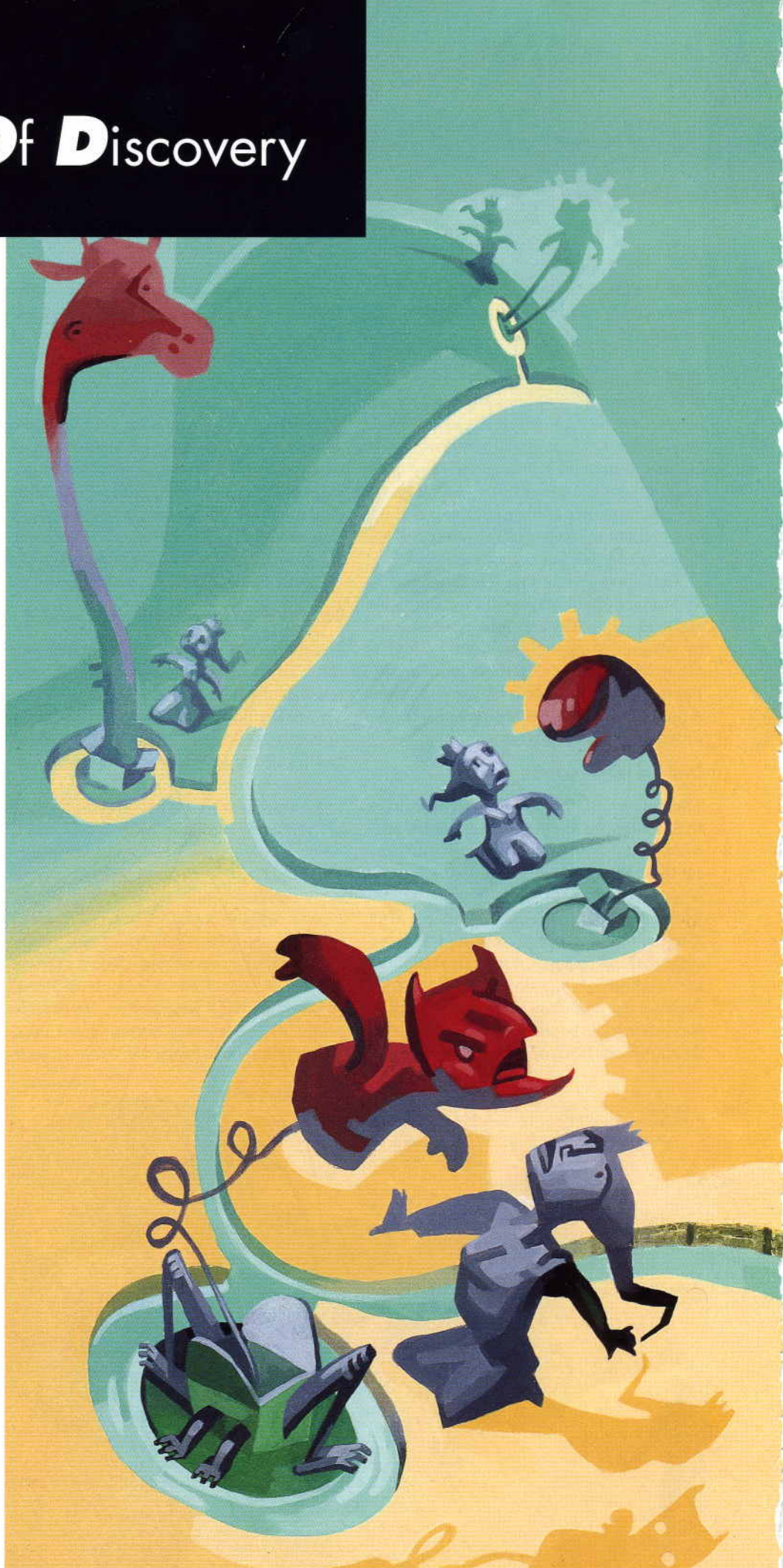
Serendipity, The Grace Of Discovery

By Roald Hoffmann
Illustration Thomas Fuchs



Monday, January 28, 1754, Horace Walpole (the son of the Prime Minister of England under George II) writes a letter to his friend Horace Mann. Walpole had long admired a likeness of a woman who died more than a century before, Bianca Capello (1548-87), the beautiful second wife of Duke Francesco de Medici of Florence. Thirteen years after he first sees her portrait, his friend Mann purchases it for him, and sends it to London.

Walpole plans a frame for the portrait, with a label that has on one side the coat of arms of the Capello family, on the other side that of the Medicis. In a 1578 Venetian book he finds two coats of arms of the Capellos. In one of them a fleur-de-lis is added to a blue ball. He recognizes the fleur-de-lis as a Medici emblem, and he is immediately persuaded the little flower was given to the Capello family by the Grand Duke, in recognition of the alliance by marriage. He then writes: "This discovery indeed is almost of that kind which I call serendipity, a very expressive word, which as I have nothing better to tell you, I shall endeavor to explain to you: you will understand it better by the derivation than by the definition. I once read a silly fairy tale, called *The Three Princes of Serendip*: as their highnesses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The Three Princes
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(Horace Walpole, 1754)

Serendipity...

...is a precious gift, but we should not forget

travelled, they were always making discoveries, by accidents and sagacity, of things they were not in quest of..." Serendip was one Arabic name for Ceylon. The book Walpole read, which went through many editions, was a collection of oriental tales, loosely translated (in the 16th century) from Persian into Italian by one Christoforo Armeno. Oriental romances of adventure and cleverness were in the air – it's conceivable that Walpole was also influenced by reading Voltair's Zadig, published just a few years earlier. When I read Walpole's letter in its entirety (I knew before only the Serendip coinage), my heart jumped. For I also loved Bianca Capello. No, not in life (neither did Horace Walpole), but as Walpole did, in a portrait. "Mine" hangs in the Palazzo Vecchio in Florence. It is a 1570 alchemical painting by Stradanus (Jan van der Straat). I show it in nearly every general lecture I give, saying with a smile that it is the earliest portrayal I know of the sociology of a chemical research group: off to one side is the bespectacled master alchemist, doing no work, but telling others – the Grand Duke and my Bianca Capello at center – what to do. Around them, lovingly painted, the hard-working alchemists – today's graduate students.

Dropping old paradigms

Once upon a time (1986), chemists Hans J. Lang and Heinrich Englert at Hoechst became interested in the sodium (Na+) hydrogen (H+) exchange (therefore called NHE) system, a fine biochemical machine for moving about protons and sodium ions. NHE had been first described in 1976 by Swiss physiologist Heini Murer as an ion transport system in the kidney. In the early 1980s it became clear that the NHE was present in virtually every type of mammalian cell.

Pharmacologists and chemists started looking for NHE inhibitors. As often in drug development, there is no shortage of potential compounds, for chemists have certainly learned the lesson of Genesis, that we have been put on this earth to create. No, the problem is frequently the assay. In the case at hand, a promising one, using renal membrane vesicles, was developed at a nearby laboratory. Disappointingly, the sensitivity of this assay turned out to be very low.

At the same time, a colleague in the company (pharmacologist Wolfgang Scholz) was working on a completely different system, ion transport in red blood cells as an assay for diuretics. One day he was asked by a cardiocytes of rabbits on a high cholesterol diet. Remarkably, while NHE activity is quite low in red blood cells under normal conditions, there was an about tenfold increase caused by the rabbits' special diet.

Whatever the reason for the original experiment (rabbits emulating American junk-food consumers?), the Hoechst scientists saw an opportunity – these erythrocytes provided an exquisitely sensitive NHE assay, 1,000 times as sensitive as the kidney membrane vesicles.

The momentum was now there for synthetic chemists to ply their art. The old paradigms were dropped, and new classes of compounds tried. Lang thought to synthesize a molecule that mimicked the Na+ binding site of NHE. He recalled reading, some years before, a quite obscure paper by Natochin in the Russian literature, on a totally different subject, where the statement was made that a sodium ion was triply hydrated, and as such had roughly the same size and shape as a guanidinium ion.

Now that turns out to somewhat farfetched, but no matter, it gave impetus to the synthesis (and testing with the new assay) of a variety of guanidine derivatives. A new class of NHE inhibitors, the benzoyl guanidine compounds, was created. In 1988, some of these compounds, among them a compound codenamed HOE 694, turned out to be potent and specific enough to test them for reduction of brain edema. The results ... were quite disappointing.

Thus, in late 1988 Lang, Englert, and Scholz had in their hands a new class of ion transport inhibitors. But there were no known clinical indications for them! It was then decided to test one of the best compounds in a broader range of pharmacological models. One of them was the isolated working rat heart in the lab of pharmacologist Wolfgang Linz. When HOE 694 was tested in this model, Linz was amazed to find that this was about the most protective compound in cases of ischemia/reperfusion (cardiac blood vessel constriction and blood resupply) that he had ever seen.

HOE 694 was selected for development as a cardioprotective agent. But the story does not end there, for molecular biology kicks in. In 1989, the NHE gene was cloned by the group of Jacques Pouyssegure in Nice, France. In the following years several subtypes of NHE were identified. A collaboration began between the Hoechst team and the Pouyssegure group. It turned out that one subtype, NHE-1, was predominant in the other subtype, NHE-3, dominated. Compounds like HOE 694 were about 1,000 times more effective on NHE-1 than on NHE-3. So, finally, it was understood why the erythrocyte assay had worked so well and the renal membranes less so!

All of those many laws that characterize the infinity of failures facing human beings apply to pharmaceutical research as well.

In early 1992 it emerged that HOE 694 formed a metabolite which precipitated in the kidney, where it caused obstruction and inflammation. Rapidly, a strategy was devised to construct compounds that were metabolized in a different way, but still effective on NHE-1. As soon as mid-1992, a new compound, was synthesized by chemist Andreas Weichert and its development was underway before the end of the same year. Now this compound has reached a late stage of clinical development.

Hallmarks of serendipity

Chance favors the prepared mind, is what Pasteur said, or more precisely: "Dans les champs de l'observation, le hazard ne favorise que les esprits préparés." Indeed, it is hard to think of a better expression of serendipity as one views the incredible concatenation of intentional and chance events in the development of NHE inhibitors.

And yet, and yet ... the prepared mind is certainly far from all. There must be some distinct human quality/qualities that allow chance to lure the well-prepared mind off the beaten track and into a new world. Here are some things I see.

Curiosity, wonder, openness: The mind must be wide open to the possibility of the unforeseen connection. Georg de Mestral walked down a country road in the 1940s, and came back covered with cockleburs. Many of us have had that experience. But de Mestral went beyond mere wonder at this brand of natural adhesion, and from its small hooks and loops came up with the concept of a fastener eventually marketed as Velcro.

The importance of being (doubly) earnest: Many serendipity episodes seem to begin with intense concentration on a seemingly insoluble problem. The problem is then mentally shelved, another pressing need addressed. Meanwhile, neural pathways are being burnt in. They wait patiently, shy traps for new ideas. Minutes or years later a connection is made, as if by magic. Intent cogitation on one problem is insufficient; I think one must think deeply on, or experience, at