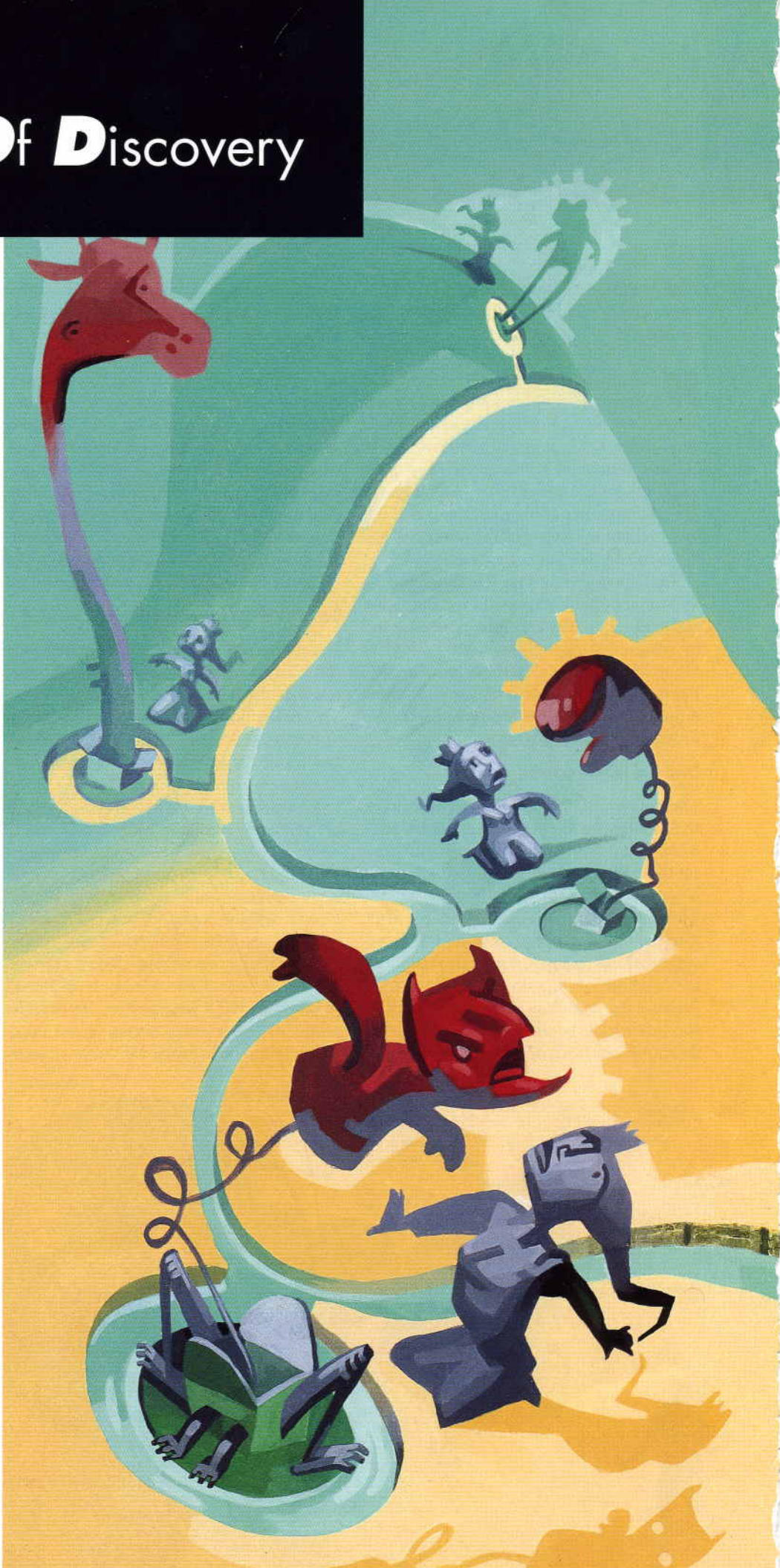


Serendipity, The Grace Of Discovery

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



"I once read
a silly fairy tale, called
*The Three Princes
of Serendip*: as their
highnesses travelled, they
were always making
discoveries, by accidents and
sagacity, of things
they were not in
quest of..."
(Horace Walpole, 1754)





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 cardio-

logist 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 far-fetched, 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



sang as a young woman in my university's chapel. In her recent book *Silent Thunder*, she recalls standing near the organ during a performance of Bach's *Passion According to St. Matthew*. She writes: "The organist pulled out the great stop and the air around me began to shudder and throb. The bass notes descended in a scale. The deeper they went, the slower the shuddering became. The pitch grew indistinct or muffled, yet the shuddering became stronger. I felt what I could not hear."

More than thirty years later she stands near some elephants and feels faint throbbing or shuddering. She remembers the organ at Cornell. She thinks, "Were the elephants calling to each other in ultrasound?" She and her colleagues build this feeling, of "distant thunder," into an understanding of elephant communication.

Hard labor, or at least washing the dishes: Could it be that for a serendipity discovery one has to have the hands, and feet, and muscles working too, and not just the brain? I think so. The mind too often gets caught in a rut; there is no better way to disconnect than to do physical labor. Most instances of serendipity seem to involve an idea that occurs to a person when he or she is doing something. Perhaps it's simply what Charles Kettering said, "I have never heard of anyone stumbling on something sitting down," but I would argue for a special role for a mind-motor link.

The care and feeding of laboratory instrumentation, having much in common with that of hard-to-grow plants, is one prescription. Experimental work often has that mantra-like quality to it, its own logic and rhythms. And instruments are at times almost playfully turned unto unknown objects, with results that may be of immense value. So Antonie van Leeuwenhoek, a draper and haberdasher by profession, takes off from a glass used to inspect cloth, builds a microscope, and discovers microbes.

Physical activities are salutary prompts to creativity. Weeding in the garden, washing dishes, ironing is where many people get good ideas. In the United States and Germany this would be a great argument for getting men to do more housework!

Chance by design

What can be done to foster serendipity? Even if creativity is the most mysterious of human qualities, we know that the field in which creation is the crop can be tilled and fertilized. Things can be done right. And many more things can be done wrong. Gladyshe said

and hands had better be prepared. If an individual can grow expert in more than one specialty, all the better. An organization, such as a pharmaceutical firm, can easily assemble a group in which different individuals have varied expertise. But the company had better create the multidimensional analogue of a nervous system to make the connections between the knowledges of the individuals, the connections that exist naturally within one human mind.

The potential for chance needs to be institutionalized. So seminar speakers in very different fields should be regularly brought in. And the habit inculcated of going to those seminars, even if they seem far afield from one's specialty. The worst that may happen is that one falls asleep after five minutes. But then one wakes up from that high quality nap, and all of a sudden an idea is taken in.

A cheerful, welcoming, comfortable setting for a coffee or tea dispenser is a *sine qua non*. I think small Italian bars should be carefully seeded around the globe. Throw in a few paper pads.

It is very important to create the psychological conditions within a group of mutual acceptance. The foundation here is joint work, separate expertise, and a reward structure that honors the group as well as the individual. A psychologist, Carol Kimball remarks that it is essential to cultivate the habit of not dismissing ideas as crazy. To be sure, often the way a real dialogue starts is when somebody risks an idea, and another group member says "That's crazy!" It is important that that doubter not be in a position of authority, lest his or her opinion be taken as fiat; wild ideas have a way of sinking down for a while and then rising in the subconscious (or it's equivalent in a group setting) to be reincarnated as possibilities.

Why serendipity pleases us so

Why are we satisfied with chance (in serendipity)? We don't have that high a regard for chance *qua* chance. We lose at roulette and the stock we own is usually the one going down. Our soulmate is often in the train that has just pulled out of the station.

We do like chance, and changes, romantically. The equation of serendipity couples the aleatory with real discovery; that scenario is truly fulfilling. It is best if we are actors in it, but even when it is someone else who invents Velcro® or Post-It® notes, there is nevertheless a salutary lesson, something from which we can learn. We supply the order that gives added value to chance. So we feel a need

about ourselves – chance and our cleverness are conjoined.

But there is more. Once upon a time, the workings of chance were called fate. Or the hand of God. The materialistic ideology of science has neatly suppressed both – fate and God. Or better said they've gone into hiding, for I believe they are unsuppressible human psychic strategies for coping with the world. Serendipity now plays a most curious function, for it reconnects, in a strange way, the scientist with the spiritual universe.

As Sylvie Coyaud writes: "Serendipity is the ultimate gift, because it talks to you but has no bond, no mutual indebtedness, you can't reciprocate or acknowledge it with thanks to any one, unless you have a god. It is the name scientists, materialists and others of the secular persuasion had to give to gifts of gods, if they were to rid themselves of god and that lazy deity, chance, now called randomness."

Mary Jo Nye has beautifully captured the special sense we experience when we partake in a serendipitous discovery, as that of feeling like "the favored child." The reason we are essentially never unhappy with serendipity stories, even if we are not the ones who were graced by discovery, is that the experience is truly accessible. It can happen to us, it does happen to us.

Telling stories of faith and hope

No one can miss the excitement of the story of the discovery of NHE inhibitors. Indeed, not the least pleasure of serendipity scenarios is that they allow the ancient human desire to tell stories to surface precisely in a human activity (science) that sometimes has the conceit of claiming that it can abolish the transformative, deeply spiritual power of narrative. A typical account of serendipitous discovery has misfortunes aplenty, mountains to climb or tunnel through, the heroic figure who turns chance into cleverness. In these remarkable narratives there are curiously few villains, and often much wit.

The pleasures of serendipity are those of myth, of fishermen telling each other stories. Here, à propos, is an apposite quotation from the much maligned American president, Herbert Hoover: "A fisherman must be of contemplative mind, for it is often a long time between bites. He is by nature possessed of much faith, hope, and optimism or he would not fish; for we are always going to have better luck in a few minutes or tomorrow."

There is something that fishers for new drugs can learn from this story.