# And today we have naming of parts.

*...Today we have naming of parts. Japonica*
*Glistens like coral in all the neighbouring gardens,*
*And today we have naming of parts*.

So wrote Henry Reed in 1942, in a poem that contrasts the enticing beauty of the natural world with the mind-numbing tedium of military training in correct nomenclature. The word 'nomenclature' is unlikely to set many hearts racing even in the most promising of contexts. Imagine, then, spending a whole autumn weekend in Paris, not touring the delights of the Champs Elysées or the Louvre or the Seine, but in a basement room of a business hotel, discussing thorny topics for the Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR [1]), an offshoot of UNESCO. Sounds like fun? No? Well, it is!

This meeting happens every year, and has for a long time been hosted in Paris thanks to the generous sponsorship of *Laboratoires Servier,* who play no direct role in the proceedings but who help to pay the hotel bill, to give something back to the science base on which all pharmacology researchers and companies depend. Ostensibly, the business of NC-IUPHAR is to decide the official names for drugs and the targets in the body to which they bind because, without an internationally agreed set of names, pharmacology would be in chaos. Naming things is difficult without a full understanding of what they do, yet it is essential that some formal name is given while the research into how things work continues, to limit the scope for confusion. It is essential, therefore, that new molecules are placed firmly into the context of leading-edge research, and for that reason much of the time of the meeting is spent with some of the world's leading pharmacologists describing and discussing the thorniest and trickiest problems of the field, presenting stories of great hope and, about as often, of dashed hopes for promising drugs that turned out not to be as effective or as safe as they looked early in the research process. These weekends are therefore full of high drama, of stories as gripping as any to be found in a novel, of ideas and counter-ideas, of possible truths half-glimpsed in the light-and-shade of incomplete data, all set against the backdrop – as we never forget – of the lives and the deaths of real people, and of the diseases any of us may face as the years go by.

Let me take you, then, down for one day into the meeting room, where a long, U-shaped table is

crammed with papers, a projector, strong coffee, and places for 23 of the world's leading experts in pharmacology, some of whom have flown half way round the planet to be here. Alright, 22 of the world's leading experts in pharmacology…. and me. People bustle in and sit down, there is the usual problem persuading the projector and laptop to play nicely together, and introductions are made, although everyone seems to know everyone else anyway. I would list the participants here, but we have a code of practice of not mentioning specific people or specific drugs and targets outside the meeting, because some participants are presenting commercially sensitive material.

The scientific session opens with a session on the challenges of obesity, diabetes and adiposity. A researcher opens with an overview of the pathology of these complex conditions, and focuses on one particularly important hormone pathway that, arguably, sits at the centre of the disease. This pathway turns out to be under-active in people with type II diabetes. It is be possible to stimulate the pathway with injections of its natural hormone and this is very effective against the main problems of the disease, but the natural hormone is very short lived in the body so it is impractical for everyday use. Thoughts therefore turn to prospects for developing a drug that will substitute for the hormone, that will stay in the body for a long time and that will, ideally, be able to be taken by mouth instead of being injected. The discussion rapidly becomes complicated and fascinating. It turns out that the receptor for the hormone triggers several different pathways inside cells, and different drugs stimulate the pathways unequally, one stimulating pathway A more than B and C, and another stimulating C more than A and B and so on. There follows a detailed discussion of 'biased agonism', as this phenomenon is called, of strategies to develop drugs with desired pathway biases and, of course, of systems of nomenclature that can capture this information. The conversation broadens further, with a discussion of whether some drugs that have always been thought of as inhibiting things ('antagonists') may actually be very biased agonists, pushing activation away from the pathway being measured into another one. Could this explain some side-effects?, we wonder.

Another speaker presents a quite different idea for tackling the high blood sugar of type II diabetes, by inhibiting the action of a sugar transporter that the kidneys use to recover sugar from urine before it passes out to the bladder. It turns out that this strategy shows an unexpected benefit to cardiovascular health. One researcher in the room, a serious athlete with a strong interest in both evolution and the physiology of exercise, offers a possible explanation based on the environment for which humans first evolved. There follows another fascinating discussion on the role of the day-

night clock in type II diabetes. Observations had been made in mice with a type II diabetes-like illness that their day-night rhythms were odd. Furthermore, a drug that interfered with a pathway that couples day-night changes to the metabolic activity of cells of the body was very protective in mouse models of type II diabetes, mainly because the mice burned up more energy, including fat, to make heat. This looked like being a very exciting story: could this simple drug be equally good for human patients? Studies were made on human type II diabetes patients to find out if they too showed odd day-night rhythms as the mice did but, alas, there turned out not to be the slightest evidence for it. Worse, an unrelated study showed that messed up day-night rhythms were associated with development of cancers in humans, so treating people with a drug that would alter the coupling of day-night signals to cells would seem to be a silly thing to try. These years of very exciting research on mice by a talented team may, it seems, be destined not to help humans at all. There follows a very interesting discussion on the problems of extrapolating mouse data to humans, ranging from the different physiologies of the animals, to the fact that lab mice are kept in a very clean environment free of disease while humans are out in the messy, dirty, infectious world, to the fact that most mouse experiments are done with young mice and most human diseases afflict the old. This leads to some sensible, detailed planning on alternative ways of working in the future.

The session on diabetes and obesity over, we all retire to the coffee area and make a dash for the pastries: to heck with irony!

The next session of the day is devoted to planning future enhancements to the public database that holds the current nomenclature of NC-IUPHAR [2], and to the challenges of naming genes. The latter aspect is led by a senior person in the Human Gene Nomenclature Committee, who first tells the story of the shrinking genome (there now seem to be only about 19,000 human genes: the others once thought to be genes mostly lead to no product, and are pseudo-genes). This raises the fascinating problem of classification of genes that are pseudogenes in most people but that are actual working genes in a few of us. It also raises the by-now familiar imperative that we stop viewing patients as being the same, and actually find out what genes they have before prescribing. Doing this will be expensive in the short run, but probably very economical in the long-run and will prolong many lives ('prolong' because nobody in the trade talks of 'saving' lives: doctors cannot confer immortality, but only stop *this* problem killing someone, leaving them alive to face another problem, at a later day).

After lunch comes a session on an idea for using existing drugs for new purposes – always attractive because these drugs will already have gone through safety testing. A researcher working on an ion channel in the brain presents evidence that mutations in the channel that make it open too easily can cause autism, impaired learning and epilepsy. This family of channels has been known for years to be important in the heart and inhibiting the family has been the basis of a very successful range of medicines used to prevent high blood pressure. Would there be any possibility of using these drugs against autism? We are shown a great deal of original data that tell a gripping story. First come the data proving the idea in cells in culture, then come data showing a complication in the way that the drug inhibits over-active channels: not as well as it binds to normal ones, it turns out, which is a disappointment. Then the coup-de-grace: because of this effect, the concentration of existing, tested drug that would be needed to inhibit the autism in the brain would have much too large an effect on the similar channels of the heart and would be dangerous. Hope is not lost completely, but a new and better drug, that interacts only with one precise type of channel, will be needed.

The subject then changes to cancer: someone presents a story of the discovery of one channel that is almost unique to the membranes of embryonic cells and cancer cells. The only place it is normally expressed in an adult does not need it. Beautiful images are shown that apply to the body a tracer that concentrates only in cells with this channel: through the tracer, we see cancers in PET-scans of patients, shown in brilliant clarity ('brilliant' is not mean to be tactless: information like this can make a world of difference to the success of surgery and radiotherapy). But imaging is not all. Surely these cancer cells, of many different types of cancer, would not make this channel if they did not need it. This thought triggered a set of experiments in mice with cancer that showed a really dramatic prolongation of life if the mice were treated with a drug that blocks the channel. Of course, everyone knows that it is easy to cure mice of cancer and often much harder to cure humans, but the results look impressive nevertheless, and a phase-I human trial has begun. We go to a tea break feeling rather buoyed up.

The final session of the day has two topics. One is on the basic biology of inflammation – a process at the heart of many diseases – and the hope that understanding more about how it works will help us control its worst features. The talk includes the most incredible light-microscopic images I have seen, with objects smaller than bacteria showing up in sharp relief. The other topic is a new strategy for screening libraries of chemical compounds for effects on libraries of pharmacological targets.

The impressive, largely robotic, technology reverses the usual process of pharmacology. Normally one starts with a disease, finds a molecular target one wants to inhibit or stimulate, then tries to develop a drug. This new method is in a way more random – start with a large number of drug-like molecules and see if they inhibit or stimulate any target, and if they do, consider whether that target may be useful in any disease. The approaches are complementary and we probably need both.

At the end of the day is dinner, where the conversation continues and the restaurant staff look increasingly worried about this bunch of crazy foreigners, all jabbering away in variously accented forms of English, talking with their hands, scribbling on the napkins, and apparently being completely obsessed with finding drugs. They should be used to us, though – we do this every year.

**Links:**

1 - http://www.iuphar.org/

2 – www.guidetopharmacology.org

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