Research culture

Collaboration collections

THE ROYAL SOCIETY

Collaboration collections

A series of essays focussed on historical and contemporary collaborations and the conditions that led to their success.

The Royal Society commissioned the collection to support a more nuanced conversation around how research is done: one that celebrates the discoveries, each of its contributors, and its contribution to public life. Each essay has been written by a different author and varies in structure and form as much as the leaps in knowledge that the researchers featured in them delivered. However, the aim for all was the same; to make visible and showcase each of the different skills, talents, experiences, infrastructure, funding and, in some cases, serendipity that gave rise to their success.

The collection will build on the Society's research culture programme Changing expectations that aims to understand how best to steward research culture through a shifting research landscape. Through a national dialogue with the research community, by drawing on the experiences of our past and present, and exploring potential futures, Changing expectations investigates the evolving relationship between the research community and the wider research system.

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Scientific collaborations: Introduction

By Jon Turney

Science isn't science until you tell someone about it. And you must do it the right way. A paper appears in a journal - part of a system the Royal Society helped establish in the 17th century. That paper is read and refereed before publication, studied and discussed and cited afterwards. Others try and repeat the procedures it describes. Some do new work that extends the results. The whole enterprise depends on researchers working together.

But there's another, less visible, social side to science that is equally vital. That's the collaboration that allows the work to get done in the first place. We all know it's important, in principle. Yes, we celebrate individual contributions, but these days that goes with acknowledging that everyone has support networks. The biggest collaborations, like multinational squads probing particle physics at CERN or the human genome project, frequently make headlines. We hear less, though, about the myriad smaller-scale interactions that nourish new science. Nor is it easy to get a sense of how they may change as research develops.

This collection, part of the Royal Society's work on the future culture of research, is a modest effort to show some aspects of this more clearly. The topic is vast. Collaboration takes many forms, over a range of scales in time and distance. So we're not trying to be comprehensive. This particular slice through the broader landscape of collaboration describes some examples of how it works to allow new science to emerge which would be difficult, if not impossible, to achieve in isolation, and how sometimes it may not work so well.

Each essay here tells the story of one collaboration. Some are historic, some contemporary, a few still unfolding. They range over fields from research in new vaccines to genetics of diabetes to neuroscience. And even this small sample shows that the dynamics of collaboration are very diverse. If you were advising a young researcher on how to maximise the chances for joining productive collaborations, reading these essays throws up a range of suggestions.

Fran Ashcroft and Andrew Hattersley's long-standing collaboration on neonatal diabetes brings home the importance of complementary skills - one ingredient that turns people with common interests into a team, who can achieve more together than as individuals. Friendship is important too, and something extra: a spirit of generosity. That extends to believing that it matters more to get the result than apportioning the credit precisely between collaborators (easy to say, harder to do).

Like several of the teams here, they also comment on the importance of stable, and flexible funding. Ray Dolan and Peter Dayan make a similar point. Developing their joint work on brain imaging and mechanisms of reward benefitted from the fact that both had already secured long-term backing from funders who gave them freedom of maneuver. When things are moving, there is huge advantage in being able to appoint a new postdoc from existing funds, instead of waiting for a year for new money. As in some of the other stories here, the role of postdocs in cementing collaborations was also crucial. They are open to mastering ideas from several disciplines, and spending time in other labs to hone vital new skills. Such early experience seems to encourage deeper involvements in diverse disciplines later on: collaboration begets more collaboration.

The Dolan-Dayan partnership also underlines that ideas travel best in people's heads. Their own collaboration was engendered by working in labs next door to each other. Without that fortunate set-up, a collaboration-seeker has to go to where the right people are. Sometimes, that's another country. Ben Seymour, working on chronic pain in Cambridge, found that it paid to look for collaborators in a place where the culture encourages people to think like him about how to approach the problem. In his case, it was Japan where he found a stronger orientation toward application of technology.

Making that work relied on a complex constellation of enablers - a history of exchanges between workers with overlapping interests, a five year fellowship in Japan for Seymour, and, ultimately, use of labs in both countries. All that went along with identifying local mentors and installing support to manage the differences in administrative and research cultures of the two countries. This goes beyond the common view that working abroad broadens horizons, and shows how much extra work and thought is needed to realise the rewards of this kind of collaboration at a distance. Early career internships and exchanges, and a willingness to tolerate development over quite long timescales were also important.

That kind of long-term plotting is a good fit with problems that will have a similarly long life. Sometimes, though, a collaboration is an ad hoc affair, brought together to crack a puzzle that has just arisen from ongoing research. Steve Miller's account of the observation of an unexpected spectral line in the atmosphere of Jupiter, and its identification as the signature of the exotic ion H_3^+, is a case in point. As he puts it, this was a case of self-assembly, adding skills to the team as required, and pulling in new information, until they had the answer they sought. This effort, in the 1980s, ultimately involved researchers in ten countries, relying on the then new facility of email, as well as access to 1980s vintage supercomputers. It is a nice case study of observations opened up by a powerful new instrument - spectrometers linked to a telescope - calling on contributions from many other specialties to make sense of an unexpected result.

Decoding the spectral lines from Jupiter involved heavy calculation based on one of the most widely accepted, if not always tractable, theories in science - quantum mechanics applied to small molecules. Persuading potential colleagues to take up theoretical prediction when the predictions derive from novel techniques may be harder. This seems to have been an obstacle to forming collaborations to pursue one possible route to a universal flu vaccine, proposed by Derek Gatherer and Darren Flowers a few years ago. Their approach grew out of the new skills of bioinformatics, and it has been hard to get experimentalists to commit resources to test their ideas.

That's partly because, as other examples in that essay show, the full collaboration needed to make and test a flu vaccine is very extensive. This is an area where a complex

infrastructure needs to be built and maintained - including experts in microbiology, immunology and molecular biology, as well as people skilled in organising clinical trials and those who know how to manufacture vaccines in quantity. Add that some vaccines are aimed at viruses that can only be studied in labs with high containment, and the demands of the endeavour become still more complex. Collaborations like this, which are needed to prepare against major global risks, require committed investment, long-term planning and capacity building.

That investment may be in one country, or several. Rebecca Mileham's investigation of the search for super-heavy elements shows how work in two countries - the US and USSR - mired in political conflict during the Cold War, proceeded separately, but ultimately came together to bear richer fruit thanks to scientists' efforts to maintain collaboration across borders. It is heartening to find that the optimistic view - that, when it comes to science, researchers speak the same language as their colleagues wherever they work - proved true here in troubled times.

Lay people can learn that language, too - and some learn it well enough to contribute to research. This is true historically, as Sally Shuttleworth and Chris Lintott recall, and indicates that the potential for scientific collaboration is much broader than considering contemporary, professionalised, science might suggest. And as they go on to show, we are now in a new phase of "citizen science", ushered in by the internet, which is a recovery of a spirit of wider collaboration with widely dispersed, lay observers that were important in a broad swathe of past science. Some of these efforts, involving thousands or even tens of thousands of non-scientists, are probably the largest research collaborations ever mounted.

Involving other people on that scale may enable work that would be hard to achieve any other way. But we must keep room for the essence of small-scale collaboration: people talking incessantly about how to make sense of things. The main thing one of the most scientifically significant collaborations described here needed was a room for two people to share. The two in question, Francis Crick and Sidney Brenner, collaborated intensely as office mates at the MRC Labs in Cambridge for 20 years. Their contribution to science was forged through talk - but a particular kind of talk. As Brenner put it, "it was two people's minds playing on each other". That kind of relationship between equals affords an opportunity for uninhibited criticism that helps sift the important ideas from a continual flow of harebrained notions. The lessons of this celebrated partnership may be harder to apply more broadly - both were brilliant, they had an intense and close friendship, and molecular genetics at the time was at a point where enormous problems could be cracked by executing cleverly devised experiments, relatively cheaply, as long as they were guided by inspired theoreticians. It does highlight, though, as Matthew Cobb concludes in his examination of their work, that unlimited time for no holds barred discussion is not a luxury, as it sometimes seems today, but can be the most important spur to progress.

In the end, as the Crick-Brenner history reminds us, collaboration is personal. But it is influenced by the conditions in which research work is done. Understanding those conditions better can underpin the formation of teams with a stronger chance of advancing new work than individuals working alone. We hope this booklet helps inform some of those conversations.

A fine balance: the ATP-activated potassium channel and neonatal diabetes

By Georgina Ferry

A collaboration between electrophysiologist Frances Ashcroft and diabetes researcher Andrew Hattersley has freed thousands of children and their families from the tyranny of daily insulin injections.

A newborn result

One day in the summer of 2003, Frances Ashcroft answered the phone in her office in the Oxford Centre for Gene Function. On the line was Andrew Hattersley, a diabetes researcher at the University of Exeter. "Fran,' he said, "I've got something to tell you, and I think you'd better sit down." He put her on speakerphone so that his colleague Anna Gloyn could join the conversation. Their news was that Gloyn, then a post-doc with Hattersley, had found a mutation associated with a rare form of diabetes that affected newborn babies. The mutation lay in a gene that Ashcroft had cloned eight years previously, and which she had predicted would be clinically important. Hattersley knew what it would mean for Ashcroft that her basic research might have implications for treatment. "There was electricity in the air," he says. "The reasons for ringing her were obvious. I knew she was the world expert, and a really nice person, and she had complementary skills. Genetics is like finding the answer in the back of a mathematics book, and she was the person who could explain how we got there."

Ashcroft is a Research Professor, based in Oxford's Department of Physiology, Anatomy and Genetics. Right at the beginning of her research career in Oxford, she had chosen to work on pancreatic beta cells, which secrete insulin in response to rising blood glucose. She adopted a new technique called patch clamping, which uses a minute glass electrode to measure the flow of electric current, in the form of ions, through tiny pores or ion channels in the cell membrane. A reduction in the electric potential across the membrane – or depolarisation – causes the cell to release insulin.

"I spent the first few months trying to figure out how glucose might cause membrane depolarisation', says Ashcroft. "Previous work suggested a reduction in potassium ion movement across the cell membrane might be involved, so I set out to look for a potassium channel that was closed by glucose metabolism." She recorded what happened to ion channels in an intact beta cell. "I knew I needed to have metabolism intact", she says. She then manipulated the glucose concentration outside the cell, and looked at how it responded.

In 1984 she published her discovery that glucose induces potassium (K) channels to close. These normally allow potassium to flow out of the cell down its concentration gradient (higher inside than outside the cell). Potassium channels play all sorts of roles throughout the body, setting off signalling cascades that drive cellular functions. If the channels are closed, potassium ions accumulate in the cell, reducing the electrical potential across the cell membrane. Some calcium channels are sensitive to this change in voltage: they open, allowing calcium ions to flow into the cell down their own concentration gradient (higher outside than inside the cell). In the beta cell, calcium enables tiny packets of insulin to fuse with the cell membrane and release the hormone into the bloodstream.

The intermediary between glucose and the potassium channel turned out to be the energy-carrying molecule adenosine triphosphate (ATP). The ATP-sensitive potassium channel , or KATP channel as it is known, is a complex membrane protein with a binding site for ATP, and Ashcroft has been working on it ever since.

Getting to know the families

While Ashcroft was developing her research, Hattersley was just qualifying in medicine. He went on to research on the genetics of maturity-onset diabetes of the young (MODY) in the Oxford clinical research laboratory then headed by Robert Turner. The condition is hereditary, and the work involved collecting DNA from large families. “I got to know Fran as [she was] a leading diabetes researcher in Oxford”, he says. In 1992 Hattersley was one of the first (almost simultaneously with French researcher Philippe Froguel) to discover that a mutation in the gene for glucokinase, an enzyme involved in glucose metabolism, was associated with MODY in some families. This was the first single gene defect known to result in people getting diabetes. “After I presented this result, I remember Fran came up to me and talked about it – she was very excited”, he says.

Soon after this Hattersley left Oxford for two years in Birmingham, before being appointed as a clinical consultant at the Royal Devon and Exeter Hospital, with one day a week for research at the University of Exeter. The university and hospital established Exeter’s first medical school in 2000, and with his colleague Sian Ellard he set up a joint research and diagnostic molecular genetics lab at the hospital from scratch.

A chance meeting at the International Diabetes Federation Congress in Mexico City in 2000 took him in a new direction. Over breakfast he heard from a Dutch clinician, Jan Bruining, of rare cases of children who were diagnosed with diabetes soon after birth. The indications were that this was not Type 1 diabetes, which is an autoimmune condition and so cannot develop before the immune system is mature. Neither did it usually run in families, so they would not be able to use large pedigrees to pin it down.

“Jan said we should set up an international [DNA] collection’, says Hattersley. So they established the International Society for Paediatric and Adolescent Diabetes (ISPAD) Rare Diabetes Collection, as “a dating agency for diabetologists and geneticists”. Clinicians worldwide who encountered neonatal diabetes – cases account for just one in 100,000 births – contributed samples, so that geneticists could search for candidate genes. Because parents of children with neonatal diabetes were almost always unaffected, it was probably caused by a spontaneous mutation in a gene critical for insulin secretion. The children had to have insulin injections four to five times a day and constantly monitor their blood glucose, a tremendous burden to them and their parents.

The vital channel

Meanwhile, back in Oxford Ashcroft had continued her studies of the KATP channel. By the mid-1990s her own and other groups were able to identify the channel proteins and clone the genes that encoded them. The channel stood revealed as a complex of two different kinds of subunit: Kir6.2, which forms the pore in the membrane, and a larger regulatory subunit, known as SUR1 because it was the site of action of a class of drugs called sulphonylureas that had been used in tablet form to treat Type 2 diabetes since the 1950s.

Once the genes were cloned, Ashcroft could begin to test the effect of different mutations. She quickly found that ATP binding to Kir6.2 caused the channel to close, while the regulatory subunit was not only the drug-binding site but also involved in metabolic regulation of channel activity.

The system was so finely balanced that only small changes in the way the channel worked could have marked effects on insulin secretion, and hence cause diabetes. Moreover, any mutation in the Kir6.2 gene that stopped the channel from closing would mean children were diabetic from birth. But to begin with, clinicians told her that such children did not exist. “I remember giving the Dorothy Hodgkin Lecture at the Diabetes UK conference in Glasgow in March 2003,” says Ashcroft, “and saying that I thought mutations in the KATP channel could be associated with diabetes, and that I expected patients to be born with diabetes. After the talk Andrew told me such patients did exist, and they were screening their DNA for the gene that we had cloned, but had not found any mutations yet.”

“All collaborations, just like in any relationship, go through some patches that are more difficult than others, but that’s why it’s good to be good friends. And of course,’ she goes on, ‘it’s not just Andrew and I. These days scientists work in large teams, and we’ve been very lucky to have many wonderful people working with us who have contributed to this story’.”

Professor Frances Ashcroft FRS

Anna Gloyn had in fact chosen to search for Kir6.2 mutations two years previously. She drew a blank with the first few patients, but persistence paid off. Later in 2003, with the extra samples from the ISPAD collection, she found two unrelated patients from the Netherlands who both had the same mutation in the Kir6.2 gene. Both sets of parents were diabetes-free. “We knew it was a spontaneous, de novo mutation, and so it must be the cause’, says Hattersley. That was when he called Ashcroft, asking her to examine how this mutation affected the KATP channel.

“I was unbelievably excited”, she says. “It was 24 July, and many people were about to go on holiday, so I suggested maybe holidays should be cancelled! Happily, people in my team like Peter Proks and Jenny Antcliff were equally excited and agreed. We already had the system running

for looking at mutations in the KATP channel, we already knew some of the residues that were involved in the putative ATP binding site, we had a molecular model of the site and had done lots of mutations, and we knew exactly how to go ahead – so we were able to dive straight in." The experiments confirmed that the mutation caused the channel to remain stuck in the open position, so that insulin could not be released.

We have patients waiting

Normally discoveries made by basic scientists in the laboratory take years to be translated into new treatments. But this was different. Both Hattersley and Ashcroft had realised immediately that patients with this mutation might respond to sulphonylureas. Even before he picked up the phone to Ashcroft, Hattersley had booked flights to Rotterdam to meet three people identified through Jan Bruining's clinic. The sulphonylurea drug tolbutamide had been in use for decades and is very safe, so he had no hesitation in trying it on these patients. "These were people who'd produced no insulin in their entire lives", he says. "We gave them glucose first, and got them up to 30 millimolar blood glucose – you'd normally be at about 10 – and they were up to 30 with no insulin secretion at all', he says. "We gave them intravenous tolbutamide, and there wasn't immediately any dramatic result. But we took samples over the next ten minutes, and showed that in the presence of tolbutamide these people produced insulin for the first time."

Soon afterwards he became aware of an adult from Brazil who had a $K_{ir}6.2$ mutation: he had been diagnosed with diabetes at three months, but because his parents would struggle to afford insulin they requested something cheaper. His doctor had tried sulphonylurea tablets, even though they had no role in treating insulin-dependent diabetes. At 46 he was still on tablets, with far better glucose control than other patients who were on insulin. So Hattersley knew that long-term treatment with sulphonylureas should be possible. Collaborating with clinicians around the world, he began to investigate what dose of drug was needed in order to withdraw insulin treatment from patients with neonatal diabetes.

Meanwhile Anna Gloyn had redoubled her efforts to screen patients in the ISPAD collection and elsewhere. Of 29 neonatal diabetes patients, she had found ten with mutations in the $K_{ir}6.2$ gene. Some of them also had marked neurological complications including epilepsy, muscle weakness and developmental delay. Ashcroft had predicted this, based on the expression of $K_{ir}6.2$ in muscle and brain as well as the pancreas, and it turned out to be a major problem for these patients.

With Ashcroft's laboratory findings, the clinical data were impressive enough for a paper in the New England Journal of Medicine. When it came out, in April 2004, the Exeter scientists organised a party in a waterside pub in nearby Topsham to celebrate. Ashcroft's team came, and Bruining came from Rotterdam. He brought with him a video of a two-year-old boy called Euyel who before his mutation was detected had been unable to sit unaided. The video showed the remarkable effect of just a few weeks of treatment with tablets: he was now able to walk. It was an emotional moment. Ashcroft and Hattersley subsequently showed the video on many occasions – Oxford's Regius Professor of Medicine, John Bell, even used it as part of his presentation to persuade then Prime Minister David Cameron to launch the 100,000 Genomes Project in 2012.

It was to be the first of many such transformations. Ashcroft tipped off the Daily Telegraph's science editor, Roger Highfield, about their studies. The mother of a British five-year-old called Jack saw Highfield's story and got in touch with Hattersley. Her son had neonatal diabetes and wasn't yet talking. Hattersley's lab screened his DNA and found the mutation: he was put on the tablets, came off insulin and within weeks he said his first words.

The Exeter lab offered free genetic testing to anyone in the world with neonatal diabetes. By 2006, teaming up with testing centres in France and Norway as well as the basic scientists in Oxford, Hattersley and his colleagues were able to show that of 49 patients with mutations in the $K_{ir}6.2$ gene, 44 had come off insulin and were doing well on tablets a year later. "The emails we received were so touching', he says. "We heard about the first time a child had been on a sleepover, or on a school trip. I never dreamed that would happen."

Ashcroft's team in Oxford began to tease out the subtly different effects of different mutations in the $K_{ir}6.2$ gene, and also in the gene for SUR1. They assessed the response to sulphonylureas in the lab, and found it could predict the clinical outcome accurately. If Hattersley found a patient who wasn't responding to tablets, but Ashcroft's tests said they should work, they would recommend increasing the dose. The only disappointment was that the tablets did not provide relief from the more severe neurological symptoms suffered by some patients. Ashcroft is continuing to explore this with a transgenic mouse expressing the mutation most often associated with neurological problems: it seems that sulphonylureas do cross the barrier from blood to brain, but are rapidly pumped out again. "The mutations also taught us a great deal about the channel itself", Ashcroft says. "For example, they helped identify the site at which ATP bound,' (a finding that was confirmed when the structure of the KATP channel was solved in 2017), "and they identified parts of the channel that move when it opens and closes."

In 2009 Ashcroft proposed an international meeting that would bring together the clinicians, the basic scientists, the patients and their families. "I thought it was important for people whose children have this rare disease to be able to talk to each other", she says, "and it was important to me that we, the scientists, were able to meet the people our work had helped." The Wellcome Trust funded the meeting (Ashcroft says it was the fastest funding decision she has ever known), and it took place in the halls of the Royal Society. It was very emotional for all of them: 100 patients from around the world came with their families. Hattersley spoke about the genetic and clinical aspects, Ashcroft spoke about the basic science, and the third speaker was Laurie Jaffe, the mother of Lilly, an American patient whose life had been transformed by transferring to tablets.

Jaffe, who is very media savvy, had made sure the world knew when her six-year old daughter switched off her insulin pump for the last time in 2006. Lilly's story had made the front page of the Chicago Tribune, and Jaffe and her husband Mike went on to commission a documentary film, Journey to a Miracle (2015), publicising the fact that many (if not most) of the 500 patients with neonatal diabetes were not getting the right treatment.

In the film, Hattersley says “A personal story had far more impact than anything that could be done in conferences or lectures, and I think to see how rapidly America has moved to the very forefront of research in neonatal diabetes is an outstanding example of why patients matter.” Ashcroft agrees. “We should give a lot of credit to the parents”, she says. “Spreading the word was important, especially in the US, as doctors had been slow to identify patients – the information spread more slowly between doctors than in the state-funded healthcare systems of Canada and Europe. Parents have supplied a lot of information, they have been willing to act as guinea pigs, and their willingness to interact with us has been amazing.”

Why it worked

The success of the collaboration owed much to the fact that Ashcroft and Hattersley were good friends with complementary skills. Each was well funded, with programme grants from bodies including Wellcome, Diabetes UK and the Medical Research Council, and they did not need to apply for grants specifically to fund the collaboration at the start of this work. “My Wellcome grant was originally on genetic diabetes and birthweight,’ says Hattersley, “but we just transferred it. We could not have something as exciting as this and stop and wait for money.”

Both emphasise that the collaboration embraces their respective research teams. Most of the interaction has been by brief visits, phone and email, but Sarah Flanagan from Exeter spent four months in Oxford learning how to do patch-clamping, and Ashcroft and her lab colleagues have made many visits to Exeter for meetings. Hattersley thinks that the nature of such long-distance collaborations makes for high quality, because “you have to transmit a lot of information in the time you’ve got together.”

“What’s truly important is that you like the person – not just respect them as a scientist, but be prepared to spend time with them”, says Ashcroft. “That requires generosity on both sides. Sometimes you will not be the first or last author on the paper. You have to be prepared to work as hard as they do, you have to be prepared not always to be listened to. All collaborations, just like in any relationship, go through some patches that are more difficult than others, but that’s why it’s good to be good friends. And of course,’ she goes on, “it’s not just Andrew and I. These days scientists work in large teams, and we’ve been very lucky to have many wonderful people working with us who have contributed to this story.”

Friendship and mutual respect paid off when it came to writing up papers. “We wrote our bit and Fran wrote her bit”, says Hattersley. “She’s a very good writer, and would help with the overall writing. So we had a paper that didn’t just say “This is the answer at the back of the book”, but also “This is the reason”, and if you can put it scientifically everyone is much happier.”

“The more you collaborate’, he says, “the more you realise that collaborations that work are always win-win, not win-lose. But you need to learn that.’ He recalls that when he was starting out in genetics, the research director of the British Diabetes Association, Moira Murphy, forced rival UK genetic groups to collaborate by saying she would fund research only if there was a single national DNA collection shared by all researchers in the area. “We realised that people didn’t steal ideas, and if you suggested something they improved it, and your grants were more likely to go through. UK diabetes went to another level, because instead of having six collections we had one, and then we joined up with collections in the US, and the whole thing snowballed’, says Hattersley.

But he distinguishes that kind of collaboration around a shared resource from the highly bespoke collaboration he has with Ashcroft. “That works really well for something like genetics, where you are suddenly going to come up with the answer and need to know how it works. We then contact the world expert and say “We’ve found the human disease associated with your gene – would you like to work on it?” And no one has ever said no. Fran was the first, and since then we’ve had 16 others. You could not have had enough experts in any single university to cover all the genes.”

He predicts that this kind of long-distance work with people with complementary knowledge is going to increase. “If you have hypothesis-led research then you just work within an area incrementally – you never get an unexpected result’, he says. “I think the future will see more techniques that allow you to have an unexpected result, and hence more need for long-distance collaboration with the world expert in that area.” Ashcroft adds that, on a personal level, collaborators provide a support network to share ideas with, or commiserate when grants get turned down or experiments fail. “Everybody needs a friend to phone, she says. “I’ve been incredibly lucky in that my collaborators have been amazing people. Andrew is a very good scientist, and a wonderful person, modest, gentle, really smart, wonderful in every way. Except when he’s in a boat! Then he is set on winning. When I crewed for him I ended up with some strained rib muscles – but we won the race.’

Working together, Hattersley and Ashcroft won more than a sailing race.

Further reading

Anna L Gloyn *et al.* (2004) Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit $K_{ir}6.2$ and permanent neonatal diabetes, New England Journal of Medicine 350, 1838-1849.

Peter Proks *et al.* (2004) Molecular basis of $K_{ir}6.2$ mutations associated with neonatal diabetes or neonatal diabetes plus neurological features, Proceedings of the National Academy of Sciences, 101, 17539-17544.

Andrew T Hattersley and Frances M Ashcroft (2005) Activating mutations in $K_{ir}6.2$ and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy, Diabetes 54, 2503-2513.

ER Pearson *et al.*; Neonatal Diabetes International Collaborative Group. (2006) Switching from insulin to oral sulfonylureas in patients with diabetes due to $K_{ir}6.2$ mutations. New England Journal of Medicine 355, 467-77

Models of reward: and the rewards of collaboration

Sharon Ann Holgate

When a new research unit opened next door to his lab, Professor Ray Dolan FRS had no idea that it would trigger a collaboration that changed how he approaches his own research, and reshaped the work of a whole sector of the neuroscience community.

Reward and punishment

Professor Ray Dolan is Director of the Max Planck Centre for Computational Psychiatry at University College London (UCL). He specialises in the neurobiology of decision making, looking at 'reward learning' – how the brain responds to a reward, such as a sip of a nice tasting drink or small amount of money, after learning what sequence of choices is most likely to bring the reward.

"The pursuit of rewards in our environment and the avoidance of punishments shapes how we make choices," says Dolan. 'Every organism is in the business of optimising its chances of survival. One way of ensuring this pay-off is to be adept not only at attaining sufficient rewards but also at avoiding the things that might kill you.' In humans, rewards can range from immediate and critical factors such as having enough food to eat, to deferred payoffs such as ensuring we have planned our finances for retirement.

Although fascinated by the study area, at the end of the 1990s Dolan started to feel some discontent. "I became a little dissatisfied with the research that I was doing because it was very much built around descriptive psychological models of reward," he recalls. Fortuitously, a few years beforehand the Gatsby Computational Neuroscience Unit had been set up thanks to charitable funding from the Gatsby Foundation next door to Dolan's lab. In 2002, Professor Peter Dayan FRS took over as its director. Dayan, who is still based in the Unit at UCL, is a computational neuroscientist who builds mathematical and computer models of neural processing in the brain, also focussing mainly on decision-making.

"I am interested in developing, using and hybridising ideas and models from artificial intelligence, statistics, control theory, economics and computer science with psychological and neural data," says Dayan, whose main aims are 'to understand normal and dysfunctional choice' and whose work has been applied to psychiatry and behavioural economics.

Dolan soon began to realise that his new neighbour's approach could solve his own problems. 'I was aware that Peter Dayan had carried out seminal theoretical work on reward and reward learning based upon mathematical models. Suddenly I thought: well this is the very thing I'm looking for a much more quantitative approach to things that can become a little bit nebulous.'

"I was very influenced as I think a lot of my generation were by a British visual scientist called David Marr," continues Dolan. "He'd written a book called Vision that laid down a principled prescription for thinking about how the brain works. He highlighted that the brain is different than other organs. You can think of your liver as a filter and your heart as a pump but how do you think about your brain? It's self-evident that it is more than just a lump of jelly inside your skull that consumes a disproportionate amount of the energy output of the body. You can think of the brain as a computer of sorts. It not only processes information, but in the very act of doing so it is generating this incredible sense that we have of ourselves our consciousness. So Marr laid down a formalism about how you can think about this multi-layered functionality of the brain."

This formalism consisted of three levels: the implementational, the computational, and the algorithmic level – which bridges between the other two. In the study of reward learning, the implementational level is concerned with trying to understand the physical substrate or specific structures within the brain responsible for processing reward. By contrast, the computational level addresses the question of what is the specific problem the brain is trying to solve in a particular context. For example, when a person seeks a reward the brain is trying to find a solution to a control problem. Finally Marr's algorithmic level asks what algorithms the brain uses to accomplish a particular task, such as making a choice between two potentially rewarding options.

Theory meets experiment

'Having been influenced by Marr's thinking, I realised that the work of Peter Dayan was really addressing this algorithmic component of the problem very nicely. By engaging with him I thought we could perhaps begin to bridge these levels in terms of things I was interested in,' says Dolan, who recalls how being in adjoining labs also helped.

'I was aware of a paper he'd published in the mid-90s, and then of course when he arrived at Gatsby there were opportunities to interact. The Gatsby was right next door, so not only could I speak to him but my fellows could speak to him. Peter is also very open and receptive. When my postdocs went to talk to him he was enthusiastic about their interests, an enthusiasm that rubbed off on them and kept them engaged. And of course this in turn led to some postdocs of Peter's engaging with my postdocs.'

So in the early 2000s, together with a few postdocs from each lab who were equally interested in a multidisciplinary approach, Dolan and Dayan began to collaborate.

Dolan was using functional Magnetic Resonance Imaging (fMRI) to reveal brain activity associated with carrying out a task, such as making a decision. Such functions activate neurons in specific regions of the brain. The activated neurons temporarily require greater blood flow than normal as they need additional oxygen. An fMRI scan can identify these activated neurons by measuring local changes in blood oxygenation in the brain, highlighting the regions linked to particular tasks.

'We realised that we could analyse the [fMRI] data not by using a psychological construct but [with] the very

algorithms that Peter had proposed are important in solving the problem of learning about rewards. These same algorithms could also be used to analyse the behaviour that people were displaying. So they provided a unifying framework across levels of analysis,' explains Dolan. This led to an approach to fMRI data analysis that began to rely on formal computational models.

Over to the postdocs

The wider culture that their collaborative working created permeated both labs, says Dolan. It required them to 'stand back and put trust in' their postdocs. Dayan recalls the collaboration initially got underway via one of Dolan's postdocs, John O'Doherty, who is now a professor at Caltech. O'Doherty's work, using ideas from studies of reward learning to better understand fMRI data 'became a starting point and a template' for the collaboration, states Dayan, who himself 'had long been interested in finding ways of testing and refining theories of decision-making'.

This unifying framework of theoretical and experimental study has since led to over 50 scientific papers. One key early observation – already noted in monkeys – was confirming that the peak of the response in human brain areas activated by receipt of a reward changed as a person learned about a cue that reliably predicted the occurrence of a reward. Once the pattern was learned, the response peaked at the time of the cue rather than at the time of the actual reward. In other words what the brain was learning was a prediction.

Other studies looked at decision-making in uncertain environments. They found that people would switch between two different modes of action: namely making their choice based on exploring an unfamiliar option or based on past experience. Whenever a person is faced with a changing environment they are more likely to over-ride past experience by exploring instead. Dolan and Dayan used computer models to characterise the contribution of key decision-related systems in the brain to each of these modes of acting, and the fMRI scans revealed brain activity that correlated with the exact predictions from the models.

They also studied how learning changes as people age. One experiment looked at learning based on the expectation of outcomes – investigating the expression of a 'prediction error signal' in the brain – a measure of the difference between the actual reward received and the reward the person was expecting. Participants were repeatedly asked to choose one of two fractal images on a screen, each of which had an independent probability of leading either to a reward of 10 pence or no monetary win. The experiment revealed that older subjects (over 65) learnt less well than younger subjects, and fMRI enabled the investigators to identify the specific component of the prediction error signal that was impaired in these older subjects.

The older adults who naturally performed badly in this decision-making task were then given the amino-acid L-DOPA (used in the treatment of Parkinson's Disease), a precursor of the common neurotransmitter dopamine. The performance of the treated older adults improved, such that their winnings now matched those of the non-treated younger adults. This observation suggests dopaminergic agents could be used to help improve learning and decision-making capabilities in the elderly population, though Dolan recognises that this raises challenging ethical issues.

Dolan sees this as a harbinger of wider applications. 'Taking the ideas that Peter and I developed over 15 years, we realised that many core problems in psychiatry might relate to impairments in decision making, including how one processes reward,' says Dolan. 'For example, if you are clinically depressed the things that would normally give you satisfaction no longer do so. At face value you appear to lose an ability to experience reward.' Someone with depression will not be motivated to start reading a book, for example because they have lost an ability to anticipate the reward generated by a good read. 'We also realised that the work we were doing could provide a more quantitative and rigorous framework within which we could begin to deepen our understanding of the conundrum of psychiatric disease,' continues Dolan.

Their work could potentially help patients with drug addiction and OCD, as well as older patients with degenerative conditions. 'Psychiatry is of course very complicated and so patients aren't going to be fixed through the medium of a simple equation. However many of the problems come from dysfunctional decision-making. So the more we understand about how decision-making operates, the more we can understand how it breaks. Along with the founders of this field such as Jon Cohen and Read Montague, we hope to get a better understanding of things like psychological vs pharmacological therapies, better classification of underlying problems, more accurate prognoses, and ultimately better treatments. But it's very early days,' says Dayan.

In 2017, the two collaborators shared The Brain Prize, along with Professor Wolfram Schultz FRS, a Professor of Neuroscience at the University of Cambridge, who had worked on neurophysiology in monkeys. The 1 million euro Prize, awarded by the Lundbeck Foundation in Denmark, was for 'explaining how learning is associated with the reward system of the brain'. The award highlighted how the prizewinners showed learning is linked to reward anticipation, and recognised human studies, mathematical modelling, and animal testing. Collectively their studies revealed that dopamine released with receipt of a reward is not merely a response to the reward itself, but indexes a difference between the reward we were expecting to receive and that which we actually got the bigger the discrepancy between these two quantities the more dopamine gets released.

Whilst Dayan has not collaborated on an experimental study with Schultz, he has been influenced by his work. 'From 1991 to 1992 when I was a postdoc in Terry Sejnowski's lab at the Salk Institute [for Biological Studies, in the United States], a fellow postdoc, Read Montague, and I became close collaborators. We were interested in the neural basis of reward learning and read Wolfram's papers about the unusual characteristic firing patterns of dopamine neurons in macaque monkeys. We then developed an interpretation of them in reward learning terms. We also looked at other [animal] data, for example Read found some very interesting papers on bees that we interpreted in related terms,' recalls Dayan.

Computation is key

Dolan and Dayan's collaboration has also made a lasting impact on neuroscience research in general, as Dolan explains. "I think it would be reasonable to say that the very best work that followed in the field of neuroimaging generally adopted our approach of using computational perspectives as a guiding principle to analyse the rich

data sets generated by fMRI and by sophisticated human behavioural paradigms. Hence it not only had benefits for me in terms of the work I was pursuing but also benefitted the field in general. The impetus of the approach has led to a whole culture of interest in this domain,' he says.

Both researchers acknowledge this collaboration would not have been possible without strong funding support. "We have both been fortunate to have had long-term stable funding from generous and far-sighted bodies the Wellcome Trust and the Gatsby Charitable Foundation,' says Dayan, who feels UCL's neuroscience environment and the support of their immediate colleagues has also been critical for the success of their collaboration.

While Dolan's main funding source was the Wellcome Trust, he has also enjoyed funding from a range of other sources. "I was very fortunate that I had an involvement with a private British charity, The Mary Kinross Charitable Trust. They were interested in my work right from the beginning of my career and provided an endowed Chair that has given me great freedom to pursue my research. If I need to capitalise on an idea I can immediately hire a postdoc without having to wait over a year in order to get a grant,' says Dolan. He also benefitted from other funds, for example from winning the Max Planck Research Award in 2007. "That award provided me with a very large prize (750K Euros) and I invested the majority of this on work related to reward and dopamine. That provided a very useful and flexible form of funding over five years.'

Having seen the potential for his collaborative work with Dayan to understand psychiatric disease in the elderly, Dolan convinced the Max Planck Society to invest in establishing the Max Planck UCL Centre for Computational Psychiatry and Ageing Research, which opened in 2014 and where he is the Director. The aim of the centre, co-funded by the Max Planck Society and UCL and co-located in Berlin and London, is to pursue computational inspired research with a focus on psychiatric disorders as well as the causes of cognitive change as people age a research domain now called 'computational psychiatry'.

In terms of the day-to-day mechanics of the collaboration between Dayan and Dolan, Dayan says the choice of what to study next can come "from postdocs own interests as they relate to our interests" or from "theoretical questions that are ready for experimental investigation, or experimental findings that demand theoretical characterisations".

A collaborative future?

Despite the success of the collaboration, Dolan has some worries for the future. Given the number of non-British postdocs working in his lab he fears the growth of nationalism globally, coupled with the UK leaving the EU, could threaten the current 'culture of open exchange'.

'One of the great things about scientific collaboration and exchange of ideas is that it recognises no political or other artificial boundaries. The connection is with one's fellow human beings and how intellectual engagement empowers, excites and motivates,' states Dolan. He also sees a threat to collaboration and the free exchange of ideas from what he calls an emergent 'corporate science', where large companies have research divisions in areas such as artificial intelligence and health sciences.

'The science here is not part of the traditional structures where research is carried out within universities or organisations that require funding from the state or charities,' says Dolan. Scientists working for corporations are generally required to sign non-disclosure agreements. 'The idea that scientists and the culture of science could prosper in an environment of non-disclosure seems an anathema. Corporations have the resources to hoover up young scientists from universities, offering much more competitive salaries. Some of the very best people will be tempted by the fact you can double or triple your salary. So I think there will have to be a wider discussion around the emergence of corporate science, the cultural values it promotes and the implications for the open nature of science,' continues Dolan.

For the time being, at least, Dolan and Dayan are able to continue their collaboration as they have over much of the past two decades. They each have their own take on why it has proved so fruitful.

"I think that the collaboration with Ray is so successful because he has a fantastic nose for excellent postdocs and students, and [for] interesting questions," says Dayan, who feels their skill sets are nicely complementary. 'I've also had some superb postdocs and students who have slotted right in. We were lucky in the time that we started at our collaboration questions and methods were ripe, and we have a shared perspective on many problems. Ray is also a superb manager.'

For Dolan, the collaboration's success lies in their 'shared passion for knowledge and shared interest in the people who carry out the work'. He hopes their students and postdocs will carry out 'the highest level of science possible so that they become the torch bearers for the future. Hopefully by working with us they will also learn the importance of science without disciplinary borders.'

Given the number of non-British postdocs working in his lab he fears the growth of nationalism globally, coupled with the UK leaving the EU, could threaten the current 'culture of open exchange'.

Professor Ray Dolan FRS

"It should be unremarkable that there are huge benefits to really close collaboration between theory and experiment it is an unfortunate characteristic of many areas in neuroscience that this interaction is not yet mature," Dayan adds. "The whole area of decision-making is in the vanguard and I collaborate with many other people for the same reason."

Both feel that collaboration has played a vital role in their careers. 'It is absolutely critical to my scientific work, and is also fun. I have benefited from a wide range of collaborators over the years both theorists and experimentalists. As science becomes more interdisciplinary, collaboration only becomes more important,' says Dayan.

As Dolan concludes: "The notion of the solitary genius making solitary discoveries is a myth. Knowledge is built up through creating culture that puts a premium on the pursuit of knowledge and the sharing and dissemination of this knowledge. I think collaboration is the very meat of doing science."

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Pain, memory and painful memories – an Anglo-Japanese collaboration

By Vivienne Raper

Crossing disciplinary borders is often a feature of productive collaboration. Combining that with working between different countries, and research cultures, can also enrich the work – as shown in this long-term investigation of chronic pain.

Ben Seymour first became interested in treating pain with technology while a junior doctor in Manchester. "I was struck by just how badly we dealt with pain – the commonest problem in the hospital," he says.

Around 43% of people in the UK experience chronic pain, according to a study published in 2016. For Seymour, it wasn't just common, it was a complex – and fascinating medical challenge. "There's no objective measurement for pain," he explains. "It's incredibly difficult to treat and the patients complain a lot." And empathy for pain patients spurred him to think more deeply about pain itself.

He knew that pain patients often became frustrated when their condition was treated as an excessive psychological response rather than a physical condition that could be measured with a scan or blood test. "I remember looking out of the window of the rheumatology rehabilitation ward at the old Ladywell Hospital in Salford, as the diggers moved in. I wondered why humans, supposedly nature's perfect machines, were so prone to pain," he says.

That prompted a different question: "What if pain was paradoxically among the things that makes us superior to machines, teaching us to avoid potential harm and carefully controlling our actions?" It was this idea that started Seymour on the road to what has been a successful UK-Japan collaboration. His interdisciplinary research, with a network of collaborators, has drawn on the research cultures of two rather different countries, so much so that he has fully-staffed laboratories in Cambridge, UK and Osaka, Japan.

A real pain

"Chronic pain is such a difficult problem; it defeats doctors and they shy away," says Seymour, now a neurologist and neuroscientist at the University of Cambridge. The doctor is forced to rely on the patient's subjective experience, which is often affected by their mood. Lack of effective treatments mean even when the doctor does understand the patient – they often can't treat the pain. The result, says Seymour, is "a vicious circle of frustration."

Breaking the cycle called for new insights into the basic mechanisms of pain and their purpose in the body: How do we feel pain? Why does pain hurt us? Perhaps chronic pain was a disorder of consciousness. After all, philosophers, such as Richard Shusterman, consider pain to be the height of consciousness – when in pain, we know that we're alive.

With the support of boss and mentor Professor Anthony Jones, a neuro-rheumatologist at the University of Manchester, Seymour began to run experiments between his on-call shifts. His aim was to show how pain might not be a negative, but a sophisticated teaching mechanism, designed to help us learn to avoid harm.

Getting technological

Seymour was inspired by control systems, such as thermostats in central heating systems, which use sensors to detect room temperature. When the temperature drifts away from a set point, they switch the central heating off or on. Using ideas from control system engineering, his first scientific paper in 2002 proposed a model of how the brain responded to pain based on a simple control system circuit.

Yet Seymour wasn't happy simply studying systems involved in the brain when patients experienced chronic pain. "The clinician in me also wanted to design new technologies to treat it," he says. His view of pain as an engineering problem open to technological solutions led him to seek out like-minded scientists in Japan. "When you think about technology in research," he says, "You think about Japan because Japan has been a leader in technological innovation for a long time."

It's not everyone's first thought, though. "I think UK-Japan collaboration is significantly underexploited," Seymour says. "There are complex cultural and language differences that put some people off, but also a general lack of familiarity with East Asian (Japan, Korea, China) research."

Seymour first visited Japan in 2005 after moving to University College London as a PhD student. He attended a neuroscience summer school at the Okinawa Institute of Science and Technology Graduate University (OIST). "The vision for OIST was 50/50 international researchers with a graduate school, research facilities and English language," Seymour explains. The institute wanted to attract researchers from overseas.

The summer school introduced him to Japanese research in computational neuroscience. Within a couple of years, he would develop this interest further when he moved to the University of Cambridge to work in a new computational neuroscience and machine learning lab established by Professor David Wolpert.

Wolpert had already established his own connections with Japan. "Daniel Wolpert was my competitor when I first came to know him," says Professor Mitsuo Kawato, Director of the Brain Information Communication Research Group (BICR) at Osaka's Advanced Telecommunications Research (ATR) Institute International, a private research and scientific development company similar to America's Bell Labs. In the early 1990s, Kawato and Wolpert had published papers criticising each other's results.

"But then Daniel and I were invited to an international meeting in Minnesota," he remembers. "One of the organisers held a garden party at his house and we were both invited. Somehow, the bus driver hired by the University of Minnesota lost his way, so – instead of arriving in 15 to 20 minutes – we were sat on the bus for nearly an hour. We talked about various ideas and started to write a paper together – and it's gone from there."

During the next twenty years, the pair pursued several collaborative projects, and visits between Japan and the UK. Then, in around 2010, Kawato led a delegation of computational neuroscientists on a British Consulate trip to the UK. While visiting Wolpert at the University of Cambridge, he invited Seymour to work in Japan.

"One of the reasons we invited Ben to Japan was we'd just started a new research centre," says Kawato. "We already had several foreign researchers, but not at his level. We thought his presence would be extremely stimulating and could stimulate the invitation of more people from abroad."

In 2011, Seymour applied for a five-year Wellcome Intermediate Clinical Fellowship that encourages work overseas to learn new skills and techniques. He explains that Japan is "off the beaten track" for the fellowships, but "people in the UK and USA often think in the same way and I wanted to think in a new way."

The research centre was the Center for Information and Neural Networks (CiNet) built on the campus of Osaka University in 2013. The affiliation of researchers there is complicated, which Seymour explains is common for Japan and a cultural difference from the United Kingdom.

"Many prominent scientists have multiple affiliations with different institutes – some physical, some virtual – and it can be difficult to pin someone down to understand where they work and their research themes."

For example, the CiNET building is owned by the National Institute of Information and Communications Technology (NICT), an organisation similar to America's National Institutes of Health (NIH). Half of the staff at CiNET are employed by NICT and half by Osaka University, but there are also virtual employees affiliated with CiNET who work elsewhere. Seymour himself is affiliated with both ATR and CiNET.

He explains that the research structures are organised to fit Japanese funding, which is often top down and designed to meet national research priorities. In addition, the typical culture among Japanese scientists is that self-promotion is arrogant, making it harder to find potential collaborators online.

Benefits of collaboration

Since 2012, Seymour has worked 50:50 in Japan and the UK, with his own lab in both countries. In his small laboratory at CiNet, he has his own equipment, research budget, postdoctoral and administrative support. "This means I'm more than just a visitor in Japan," he says. "I have several collaborations and it's much easier because I have a physical presence."

He believes he's benefitted from the different research structures in the UK and Japan. NICT specialises in communications technology, including diverse areas such as cyber defence and photonics, and researchers there are interested in neuroscience to build better ICT systems.

“When you’re surrounded by experts in things such as quantum and satellite communications, rather than neurologists,” he explains, “it gives a different perspective and that’s shaped the way I think about my research.” As for navigating the complex organisational structures, “I have an administrator who helps me.”

Having Kawato, a senior scientist, as a mentor is also important. Seniority is important in Japan and “you need a mentor because there are lots of times where you don’t know how things work.” Kawato has helped Seymour navigate the NICT, who have virtually no foreign staff, as well as take advantage of collaboration opportunities.

In exchange, Seymour has helped CiNET shift its culture and become more outward-facing. As Kawato explains, “Usually young Japanese researchers are reluctant to engage in heated discussions, especially with people higher in the hierarchy, and that’s not good for research.”

Kawato explains that the hierarchical structure of Japanese science has grown up over centuries. Non-Japanese researchers “thoroughly change the atmosphere of universities and institutes and introduce new ways of scientific communications. We’re really grateful to them for this.” Seymour has tried to cultivate debate and discussion by introducing lunchtime seminars, tea talks and 360-degree feedback sessions at the annual retreat.

Seymour has also redesigned the CiNET website to present the institute as a world-famous institution. “I don’t want to criticise Japanese colleagues,” he says. “But there’s always a message from the president [on Japanese scientific websites] looking very glum [...] and the photos of people are always very smart and not smiling [...] You’d be forgiven for thinking those photos represent those people and you wouldn’t want to work for them because they look miserable.” He’s since been asked to consult on website redesigns for other Japanese research institutions.

Delivering world-class science

Seymour’s UK-Japan collaboration is also about sharing expertise. “The Japanese team is especially strong on the technology side whereas my expertise, coming from UCL and Cambridge, is in learning theory,” Seymour explains.

Kawato had developed a technique for measuring patterns of brain activity using functional magnetic resonance imaging (fMRI) in real time (within a second or so). This allows him to give people real-time feedback, and they are able to learn to alter their own brain activity towards a desired state – a process called decoded neurofeedback.

Having developed this technology, Kawato was keen to find new applications for it – something that Seymour says is common in Japan. “I often perceive a cultural tendency for people to ask: What can I do with this finding? What can I make?” he says. “As if the end point of a discovery is not the p-value or paper as it sometimes seems to be in the West, but the ability to design something that works.”

It was an ideal collaboration. Seymour’s strength in neurology complemented that of Kawato and his team. Together they – and Seymour’s other Japanese collaborators - have generated five collaborative grants and a joint conference (New Directions in Pain Neuroscience). They’ve also published 16 papers including a paper in Nature Communications using decoded neurofeedback to treat patients’ phantom limb pain. And, in a less expected turn, they have also worked with patients with phobias or Post-Traumatic Stress Disorder (PTSD). A further paper in Nature Human Behaviour explores decoded neurofeedback as a potential method to treat such patients.

Phobias, such as a fear of snakes, are often treated by exposing patients to the feared object. This has obvious drawbacks for the patient. The study aimed to use decoded neurofeedback to help treat the phobia subconsciously – without patients needing to face their fear directly.

“I’m a learning theorist so I use pain to evoke fear,” says Seymour, explaining the link between phobias and chronic pain. The team recorded the brain patterns of 17 healthy volunteers while they viewed images of red, yellow, green and blue circles on a screen. They then created two fear memories by giving them a small electric shock while seeing, for example, the yellow and red circle. One of these memories was targeted for treatment while the other was left intact.

Instead of treating the memory directly, by – for example – seeing the circles again without any more shocks, the volunteers were trained using neurofeedback. In the fMRI scanner, they were told to think about whatever they wanted. As their mind wandered, their brain displayed neural activity. Whenever their brain activity matched that associated with the fear, they were given a small amount of money.

The study was led by Seymour, Kawato and Dr Hakwan Lau, a psychologist from the United States with an interest in consciousness. “I’m not sure how the project started and grew (as is always the case with a genuinely good collaboration – where the key ideas just seem to emerge)”, says Seymour, but he credits “long video calls with lots of open discussion and open-ended thinking” for its success.

The United States link was mediated by the lead author, Dr Ai Koizumi, from ATR who had a Japan Society for the Promotion of Science (JSPS) overseas postdoctoral fellowship working with Lau in the USA. Upon returning to Japan, Koizumi wanted to do a project on fear and threat perception that was also relevant to consciousness. “It’s the sort of project that was more than a sum of its parts,” says Seymour. “The technology, the theory, and the consciousness parts just came together.”

Crucial to the success of the project were good computer tools, according to Kawato. The researchers used Adobe Connect for video conferencing and Google Docs to work on the same document across three different time zones.

Kawato also credits the Bell Labs-style funding model of ATR, which paid for the fMRI scans – the most expensive part of the study beyond their salaries – and the research model of the institute. “We have two to three test machines and, although it’s expensive, we have good access,” he says. Today PTSD patients are being treated by decoded neural feedback at ATR, according to Kawato, and they hope to run Phase 2 clinical trials within a few years.

Broadening horizons

According to Seymour, working abroad helps scientists broaden their network of contacts and that – in turn – can encourage collaborations, eventually.

"People fail to recognise that the fruition time can be long," says Seymour. "If people fund an international conference, they want to see outputs in that fiscal year, but often it takes a long time." Seymour is doing substantial research seven years after he first met the Japanese delegation.

Seymour now encourages students to intern in Japan in the hope they will form collaborations in future. "If you get people over here young, they have no fear of Japan, so at some point they will come back with something substantive," he says.

Among them is Miss Suyi Zhang, who worked in Japan for three months during a research assistantship and then visited three or four times during her recently-submitted Cambridge PhD. "It's highly efficient to collect data in Japan because everything is sorted," she says. "I write my code in Cambridge, test everything and then just run the experiment while I'm over there."

Zhang had never been to Japan before her assistantship, but understood the culture already. The long hours worked by Japanese colleagues were "really good for my career", she says and "they've also got a really good system for booking equipment compared to the UK."

"If you get people over here young, they have no fear of Japan, so at some point they will come back with something substantive"

Dr Ben Seymour

The payment system for research subjects is also "streamlined," she explains and the subjects are paid to do the pain experiments. "In the UK, there's a lot more admin involved," she says. "If I want to recruit some subjects, I have to post flyers on forums around campus, but in ATR they have a big database of people who are willing to participate." Asked if she would be willing to collaborate with CiNet and ATR researchers in the future, she says, "I've established a really good working relationship. I'd definitely collaborate with them if I had the chance."

"What makes Japan a great place to go to is the untapped resources, the great people to engage with," says Seymour. He's taking his research forward with a five-year Arthritis Research UK grant matched by funding in Japan.

He's also finally having the opportunity to explore the philosophical aspects of pain, a motivator as a junior doctor in Manchester all those years ago. "One of the first things I thought about was that, if pain is useful, autonomous robots should have pain," he says. "If you think about it as an engineer, how would you design a pain system? How would you write down the rules?"

He quotes American physicist Richard Feynman, "What I cannot create, I do not understand."

He's now beginning to build a simulation system to create robots with a pain system.

It's something – he says – he could probably only do in Japan.

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The elusive triangle: the discovery of the H_3^+ molecular ion in the atmosphere of Jupiter

By Steve Miller

It's possible to plan a collaboration in advance. But science is unpredictable, so many teams are assembled during work already in progress, as it reaches beyond the skills already on tap. Cracking the chemical identity of unidentified spectral lines from Jupiter shows ad hoc assembly in action.

In 1989, a paper in the journal Nature reported, as the title had it, "Detection of H_3^+ on Jupiter". The presence of this unusual molecular ion (a hydrogen molecule with an extra proton) was clearly an important astronomical observation to rate an article in Nature.

But what does it take to achieve "detection" of an obscure molecular species on a distant planet? The answer reveals many layers of collaboration. The paper's 12 authors included scientists from France, Canada, Korea, the UK and the USA. Not on the author list were scientists from Germany, Australia, India, Italy, Canada (again) and the USA (again) who also contributed. Unacknowledged were the people and natural resources of Hawai'i whose tacit (and unknowing?) cooperation was taken as a given.

The detection came about not during a planned close encounter with the giant planet, but instead, it relied on: a new generation of large telescopes adapted to take full advantage of the clear, dry skies above the 4,200-metre summit of Mauna Kea on the big island of Hawai'i; high resolution spectrometers in the laboratory; a new breed of supercomputers carrying out large calculations 100 times faster than before; and the coming of electronic mail – email – for communicating across the world in hours.

Nor was this a collaboration put together in advance. Rather it was a process of self-assembly: scientific skills and information were added as required, until the final result – understanding the strange new spectrum coming from the giant planet Jupiter – was finally reached.

The importance of H_3^+

Hydrogen is the most abundant element in the Universe: 90% of all atoms are either solo H atoms, or paired up as the diatomic H_2 molecule. Vast clouds of H_2 fill interstellar space, the Interstellar Medium (ISM). Most of these clouds have low temperatures, 100 Kelvin (uk), 20 K or even lower. New stars and planetary systems form there, and old stars going supernova enrich them with heavier elements.

H_3 could be the next in the hydrogen series, but is unstable. H_3^+ created when high-energy particles bombard the ISM and it is very stable, albeit chemically highly reactive because of that extra proton.

Because H_3^+ is formed when hydrogen gas is bombarded by high-energy particles it is a good tracer of where energy is being put into clouds or atmospheres of hydrogen gas. In the 1960s and 70s chemical models predicted that H_3^+ should be readily formed by cosmic rays in the ISM. But how to detect its presence?

Although H_3^+ was first discovered in the laboratory by physicist J.J. Thomson 1911, its molecular structure – H_3^+ is a perfect equilateral triangle at equilibrium - was only fully understood some 50 years later. And nearly 80 years after its original detection Takeshi Oka of the University of Chicago measured the first fingerprint lines of its infrared spectrum, created as the molecule vibrated and rotated in space. Those first few lines opened the door to getting a full H_3^+ spectrum. They also meant that astronomers could begin their search for this elusive triangle.

A focus on Jupiter

Jupiter, the largest planet, had been the focus of much attention in the 1970s. NASA had four bruising encounters with the gas giant. They found the Jovian neighbourhood full of radiation and immensely powerful magnetic fields. Charged particles from inside the planet's enormous magnetosphere streamed down around the poles to create aurorae 1,000 times more intense than Earth's. Bright ultraviolet emissions, from both H atoms and H_2 molecules, lit up the polar caps.

All this convinced astronomers to attempt follow up studies from the ground once the spacecraft had gone on their way. And Canadian John Caldwell and his Korean student Sang Kim, at that time both at the State University of New York in Stony Brook, joined this effort.

In the early 1980s, Caldwell had discovered bright auroral emission from Jupiter's poles due to hydrocarbons – methane, ethane and acetylene – in the upper atmosphere. These showed that high-energy particles, mainly electrons, could reach down to a region in the atmosphere known as the homopause, a few hundred kilometres above the cloud decks, where convection no longer mixes the atmosphere. Above the homopause, Jupiter's atmosphere is dominated by H_2 and H, and a small amount of helium atoms. Kim had been modelling the amount of auroral infrared radiation that would be emitted from H_2 molecules impacted by high-energy electrons, work he aired at various scientific meetings.

The observations that nearly weren't

Kim and Caldwell tried to get time on NASA's 3-metre Infrared Telescope Facility on Mauna Kea to look for the infrared emission from H_2, but were turned down.

So it was a bittersweet moment when a group from the McDonald Observatory in Texas, led by Larry Trafton, announced that they had detected one such emission, known as the S(1) line, albeit at much lower intensities than Kim had calculated.

At 2,000 metres up, the McDonald Observatory was only half as high as the Mauna Kea telescopes, and its infrared vision more limited. Moreover, the low resolution of the spectrometer meant that just one point out of the 30 recorded was sensitive to the H_2 line. But Trafton's spectrum was a spur for Kim to try to do better.

In Paris, Pierre Drossart, of the Observatoire de Paris, in Meudon, and Jean-Pierre Maillard, of the Institut d'Astrophysique de Paris, were aware both of Kim's predictions and of Trafton's tentative observation. Drossart was a veteran of discovering molecules in planetary atmospheres. Maillard had been developing high-resolution Fourier Transform (FT) spectrometers for use in planetary measurements; his latest creation – installed on the Canada-France-Hawai'i Telescope (CFHT) in 1980 - had a hundred times greater resolution than the McDonald observatory's spectrometer.

Kim, Caldwell, Drossart and Maillard had already discussed the possibility of detecting H_2 infrared emission from Jupiter's powerful UV auroral regions at meetings of the American Astronomical Society. Now there was urgency in attempting the observations, using the combination of conditions and sensitivity that Mauna Kea, the CFHT and Maillard's spectrometer would bring to the project. The separate French and Canadian telescope allocation committees both approved new proposals. In September 1988, Jupiter could best be seen from Hawai'i after midnight – the second half of the night. The project to look for H_2 emission using Maillard's FT spectrometer received two half nights from the French Telescope Allocation Committee and three from the Canadian.

It had taken a full day to change the telescope's "top end", which contained the secondary mirror that sent light into the instruments of the Canada France Hawai'i Telescope, to accommodate Maillard's FT spectrometer. As the team – Maillard, along with Drossart, Kim and Caldwell – drove up to the summit of Mauna Kea on September 21 for their first night, there was some nervousness: Trafton's detection of the H_2 S(1) line was hardly conclusive, and Kim's calculations of brightness made many assumptions. "But," Kim remembers, "beyond all of our expectations, we detected numerous lines including S(0), S(1), and S(2) lines of H_2, which were rather dwarfed by other unidentified strong lines." But what were these other unidentified lines?

H_3^+: a "floppy" challenge to spectroscopy

Answering that question required turning to quantum mechanics. Theoretically, we know how to use it to analyse a spectrum. In practice, the calculations needed are next to impossible, as Paul Dirac pointed out many years ago – and we researchers use approximations to make them tractable.

But even the approximate methods quickly become challenging to apply when a molecule of any complexity is involved. The H_3^+ ion is a case in point. It is unusually "floppy", which complicates the way its bonds stretch or rotate – the motions that underlie different energy states, which in turn govern the wavelengths of radiation it emits when it shifts from one state to another. Better methods for dealing with this were slow to develop, but there had been progress in the 1980s.

How a molecule behaves – vibrates and rotates – as it acquires energy depends on two factors – a "potential energy" term that tends to define what it does at equilibrium, and a "kinetic energy" term that describes its motions in space. In the mid-1980s, a German-Australian team of Wilfried Meyer and Peter Botschwina, at Kaiserslautern, and Peter Burton of Wollongong University had worked out a very accurate potential energy term; and Jonathan Tennyson, of University College London (UCL), and Brian Sutcliffe at York University had shown how to work out the kinetic energy for molecules with three atoms to very high precision.

Meyer and coworkers had also generated a mathematical function that could be used to predict the intensities of individual lines. Tennyson's team combined these elements to produce an accurate spectrum for the H_3^+ molecule that could predict higher energy lines. The calculations to do this required the use of a new, fast supercomputer, the Cray 1s. This state of the art (for the mid-1980s) machine could do in a day what other computers took two or three months. Even so, the calculations needed for just one rotational state of the H_3^+ molecule needed a whole day.

By early 1987, as one of Tennyson's new researchers, I had shown the accurate agreement of our H_3^+ calculations with Oka's measurements of the actual spectrum to some of Takeshi Oka's students in Chicago. One of them, Moungi Bawendi, went on to measure the spectrum of what is known as a "hot band", formed when H_3^+ transitions between 2 vibrational levels. In doing this, he used the Tennyson and Miller predictions for the higher H_3^+ energies.

The Tennyson group had also made another prediction that proved to be critical: unlike traditional molecules, floppy H_3^+ lines formed when the molecule jumped between 2 vibrational levels 0 and 2 – the "overtone" spectrum – would be as intrinsically strong as the lines formed when it jumped by just one.

The collaboration crystallises

Until the September 1988 observations of Jupiter, the observing team and those involved in laboratory spectroscopy and computer calculations had been working almost entirely independently. However, when it became clear that the original observing team of Drossart, Maillard, Caldwell and Kim were not able to assign the intriguing "other unidentified strong lines", some of Drossart and Maillard's colleagues suggested they might be due to traces of the H_3^+ molecular ion in Jupiter's hydrogen-laden atmosphere.

But suggestions are not proof, and astronomers and spectroscopists – like the police with fingerprints – prefer lines to be identified rather than make do with vague possibilities.

A month after the observations, Maillard started the next part of the collaboration. He contacted a friend at the Herzberg Institute in Ottawa, Paul Feldman. As that involved a transatlantic correspondence, he took advantage of the newfangled email then becoming accessible to researchers with the right connections.

The Herzberg Institute housed the world's leading spectroscopy laboratory, named after its 84-year-old director Gerhard Herzberg, who won the 1971 Nobel Prize in Chemistry for his contributions to "electronic structure

and geometry of molecules, particularly free radicals". "Free radicals" include electrically-charged molecular ions, such as H_3^+.

On November 1, 1988, Feldman emailed Maillard back: "Dear J-P, I brought up your discovery at spectroscopy tea on Friday. There was quick and unanimous agreement by GH (Herzberg himself - SM), Watson, Amano, McKellar, Vervloet and Majewski ... that you have probably observed a fairly typical emission spectrum produced in a discharge of H_2. ... It is felt that H_3^+ is not the answer ...". They were leaning in favour of the electrically neutral triatomic hydrogen molecule, H_3 .

Feldman's list of tea-drinkers was a veritable who's who of molecular spectroscopy in the 1980s. As well as Herzberg, Jim Watson was one of its leading lights, and Wotjek Majewski was a brilliant spectroscopist, who had a high-pressure discharge spectrum from hydrogen gas that had many similarities with the Jupiter spectrum. Nonetheless, Maillard pushed back in support of H_3^+ as a being a "plausible" source of the unidentified Jupiter lines and because it was "an intermediate product in many chemical reactions". "Is not H_3 less stable?" he asked.

Maillard's email coincided with a visit to the Herzberg Institute by Oka. His talk included work by his student, Moungi Bawendi, on the H_3^+ "hot band", where the molecule changed from rung 1 to 2 on its vibrational ladder. Adding the frequencies of Bawendi's hot band lines to those of the fundamental spectrum measured by Oka would enable spectroscopists to calculate the frequencies emitted when the molecule jumped two rungs at a time. These frequencies fell into the region where the Jupiter lines had been observed. Discussion raged around a particularly strong line measured, with great accuracy, at a frequency of 4777.23 inverse centimetres (cm^{-1}) (wavelength 2.093 mm). This line was at least twice as strong as the S(1) line of H_2. Still, after the discussion Feldman emailed Maillard: "I will bet on H^3 above everything else."

The email debate on the lines bustled on throughout November 1988. Then in December, there was an almost complete volte-face at the Herzberg. On December 1, Watson emailed Maillard that, having obtained results from Bawendi and Oka (which used Tennyson and Miller's), he had been able to fit 34 lines in Majewski's spectrum and ten from the Jupiter spectrum to H_3^+. But several unidentified lines in the Jupiter spectrum remained.

Cue a broadening of the collaboration. By the start of 1989 Watson was following up on Oka's suggestions of using new calculations from the Tennyson group, since they had already given accurate predictions for the Bawendi hot band lines. During January 1989, another email exchange began between Watson in Ottawa, myself in London, and Tennyson, on sabbatical leave at the Weizmann Institute in Tel Aviv. Until then, Tennyson's team had been calculating lines in several vibrational levels, but only with rotational energies of 4 or less. Watson suggested that we needed to go further, and work started to get all the way up to rotational level 12. Additionally, we used a new UCL programme to calculate not just the frequencies of the lines but their intrinsic strength. This would allow the spectrum to be used to establish a temperature, as well as a chemical composition, for Jupiter.

Now email's instant contact allowed us to make the most of time differences. Tel Aviv was a comfortable two hours ahead of London, in turn five hours ahead of Ottawa. At the end of my day, I would submit a new rotational level calculation for the Cray 1s computer to run overnight. At the end of his day, Watson would send the line frequencies and strengths of unidentified lines to me. On arriving at work, Tennyson and I would have an email discussion about the latest calculations and Watson's new lines, coming up with suggestions for identifications. Back to Ottawa would go the British suggestions, so that Watson could digest them and make final identifications, before sending a further request to London. And so the work went on throughout January.

By February 7, Watson had sent Maillard the list of 34 identified H_3^+ lines in the overtone spectrum. Drossart and Maillard, re-examining their data, emailed back more information to Watson, and then it went on to London. On February 16, Watson emailed Maillard: "I have just received from ... Miller and Tennyson the results of some new calculations for H_3^+ which suggest possible assignments of most of the remaining Jupiter lines."

These lines were visible in Jupiter's spectrum, even though H_3^+ was a billion times less abundant than H_2 in its atmosphere because, per molecule, the H_3^+ lines were roughly a billion times brighter, according to Tennyson and Miller. But the temperature – at 1,000-1,200 K – was hundreds of degrees hotter than anticipated. (And why that should be is a problem still not solved 30 years on.) It was time to publish.

Partners in collaboration, or not

After the initial spectral identifications in December 1988 by Watson, Maillard had wanted a fast publication in Nature claiming the discovery of H_3^+ in Jupiter's atmosphere. He had wanted a fairly restricted author list: the four observers, Atreya, who had been in extensive discussion with Drossart about observing H_2 and H_3^+ since before 1987 and was part of the observing proposal, and Watson. On February 3, however, Watson wrote to Maillard: "In your previous message you told me you were not going to include Wojtek Majewski's name in the list of authors. Since this work was done in collaboration, this means that you are not going to include mine either." Losing Watson's input would have seriously undermined the H_3^+ identification.

As February 1989 rolled on, the question of publication and authorship came up again. Watson had explained to Maillard that the full assignments had been possible due to the Tennyson group's unpublished results. Maillard was concerned that the author list was starting to become too much spectroscopic as against planetary science. But, on February 24, Watson explained the rationale behind his thinking as to who should, or should not, be on the list of authors.

"As far as publication is concerned, since I do not know who the other authors are, I really cannot say anything on the subject of balance. There are by now quite a number of papers in the literature on the auroral zones of Jupiter and the hot spots, and so I am not convinced that Nature is going to accept a letter whose main subject is the Jupiter aurorae. On the other hand, if the main subject is the observation of the spectrum of H_3^+ from an extraterrestrial source, it might be accepted.

I never suggested Oka and his collaborators should be co-authors, because I realised their assignments were entirely based on Miller and Tennyson's published calculations. However, if you want them as co-authors I have no objection, because they certainly provided valuable information at a critical time. On the other hand, the high J assignments are based on unpublished calculations by Miller and Tennyson, and I do not see how we can use them without including them as co-authors."

Drossart and Maillard followed "Watson's rule", more or less. The letter to Nature was submitted in the names of the four actual observers – Drossart, Maillard, Caldwell and Kim – with Watson, Majewski, Tennyson and Miller on the spectroscopy side, plus Atreya and his Michigan colleague John Clarke as Jupiter atmosphere and aurora experts. By the time referees had had their say, two new authors – Hunter Waite at South West Research Institute and Richard Wagener from Kim's old university, SUNY, were on board to make up for a "lack of freshness" in the planetary science part of the paper.

And then what?

In 1992, Oka published "H_3^+ in laboratory and space plasmas" in the *Reviews of Modern Physics*. In his section on the discovery of the H_3^+ spectrum in Jupiter's auroral regions, Oka commented: "The infrared emission from Jupiter is so intense that a brief integration suffices to see it very strongly. None of us was sufficiently imaginative to think about this possibility until it was discovered accidentally, providing yet another example of how we are all nitwits against Nature. For nearly ten years I had been searching for the spectrum in objects that are thousands of light years away while a strong signal was waiting to be observed only 40 light minutes away!"

The 1989 Nature paper promised: "H_3^+ lines could be used in future for ground-based monitoring of the jovian auroral activity and to search for this molecular ion in the interstellar medium." Indeed they could, and they have been repeatedly in Jupiter, Saturn and Uranus (though, strangely not Neptune) in the thirty years since their first discovery outside of the laboratory. H_3^+ lines had to wait until 1996 to be discovered in the interstellar medium, but they are known in dense and rarified regions and all the way to the centre of our galaxy, and used to study conditions there. There are now serious attempts to find these lines in the spectra of extra-solar planets, planets orbiting stars other than our own Sun.

Over the 30 years that have followed their first publication, the individuals involved in the collaboration have gone their separate ways. But they have also worked together on occasion, whatever the scientific agreements and disagreements they may have had in between. Collaborations where everyone is a volunteer in an ad hoc, loose structure of equal partners can form and reform as the need arises. In these days of highly organized, dirigiste and hierarchical big-project funding, research needs to maintain the flexibility for serendipitous team-building.

Further reading

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Vaccine research: where cultures collide (or stay apart)

By Julie Clayton

Combining disciplines is often seen as productive, but may not happen easily. Indeed, researchers in some new disciplines may face obstacles in contributing to problems traditionally the preserve of more estabished fields, as this tale of vaccine research illustrates.

A new flu pandemic is an ever-present threat for public health authorities to worry about. Flu viruses are constantly changing and most current flu vaccines depend on a 70-year old technology of growing each season's circulating flu strains in hens' eggs. But the protection they afford is limited to those strains. As new strains emerge, new vaccines must be created. An international panel of experts has the unenviable task of having to predict which strains are most likely to dominate in six months' time.

So it seemed like very good news when a paper was published in 2016 proposing a specification for a new, universal flu vaccine – one that might be prepared and used against all strains, year after year. It's no surprise that the paper made headlines, and remains one of the most highly cited in the journal in question, Bioinformatics.

However, since then the team (Darren Flower, at Aston University and colleagues) have struggled to find partners who would develop and test a vaccine based on their work. Part of the reason is hinted at by the title of the journal they published in. The bioinformatics field is a new approach to many problems in the life sciences. Exploiting it calls for new kinds of collaborations. But why might they be hard to establish? Answering that requires a closer look at what goes into making and testing a new vaccine.

70-year old technology

Flu viruses are constantly spreading around the world, causing an estimated 500,000 deaths a year, according to the World Health Organization. Currently available flu vaccines have to be made from scratch every year. As many as 500 millions hens' eggs are required for injecting with that year's circulating strains. The virus multiplies over several days and is then harvested and purified before being packaged for human use. This method for growing viruses originated in Australia and was developed for flu virus cultivation in the 1930s at the National Institute for Medical Research in Mill Hill, North London. This is also where the flu virus was first identified, and the earliest immunization occurred - in mice and in lab volunteers. The downside of this production method is that the supply often falls short of demand prior to the peak winter season. In the UK, priority for vaccination is given to those deemed most vulnerable – pregnant women, people over the age of 65, and those with certain health conditions including asthma or HIV infection. And because the viruses can mutate while growing in hens eggs, the vaccine stocks are not a complete match to the original strains and so may not give complete protection. For example the 2017 vaccine barely worked in older adults.

Faster production methods have gained approval – in 2012 for cell-based cultivation of whole viruses, and in 2013 for the use of recombinant technology using individual viral proteins. But they account for only a small portion of today's seasonal vaccines.

A universal flu vaccine, if one were to be created, would ideally protect against all strains, with a single shot, enabling larger stocks to be stored in advance.

Recent flu outbreaks of more deadly forms of flu have heightened fears of a new flu pandemic. Since 1997, repeated outbreaks of a very severe form of 'bird flu' have occurred in Hong Kong, caused by the H5N1 flu virus (named after the particular types of glycoproteins in the virus coat). The virus had hitherto only infected birds, including ducks and chickens, but 'jumped' the species barrier to humans – so far infecting more than 800 people worldwide and killing more than 400. Since 2013, there have also been multiple outbreaks of the H7N9 bird flu virus, infecting over 1,500 people, with more than 600 deaths. The authorities are keeping a close eye, knowing that a deadly global flu pandemic could occur on the scale of the 1918 'Spanish' flu, or the 1968 Hong Kong flu pandemics, which killed millions. Hence a greater sense of urgency around developing new and better vaccines.

Massive effort ensued to sequence the genomes of different viruses and explore ways to rapidly produce better vaccines. And the quest for a universal flu vaccine drew in the wider research community. Bioinformaticists, who specialise in computer analysis of biological data, were among those who jumped in. It was an opportunity to shake-up traditional approaches and speed up research.

"There has been lot of ground work done with genome projects and systems biology projects so that we can now do good theoretical work on the human immune system that couldn't be done 20 years ago," says Derek Gatherer at the University of Lancaster. Added to this, "the number of flu sequences deposited in the databases has gone up dramatically since 2009. So we know a lot more about variability in human flu and bird flu as well... The theory is that a single vaccine would immunise you against a whole range of subtypes, many of which we may not yet have encountered. So you would have a pre-immunity against many of the strains that have yet to enter the human population."

Gatherer joined up with Darren Flower at Aston University and other colleagues to apply bioinformatics to vaccine research. The team searched a database known as IEDB (Immune Epitope Database and Analysis Resource) and identified hundreds of small portions of the flu virus, known as epitopes, that laboratory tests had shown could spark responses in human white blood cells. Rather than aiming to generate antibodies – which seasonal vaccines do – they were hoping to trigger T cells – a different player in the immune system – to get round seasonal variation. This is because antibodies tend to target the

parts of the flu virus that mutate most often – the viral 'coat' glycoproteins haemagglutinin and neuraminidase.

The team selected viral epitopes from internal viral proteins that are normally hidden but are displayed on the surface of infected host cells. These are then visible to passing T cells, and are the least likely to mutate. They checked which ones varied the least between different flu strains, and what proportion of the US population, for example, would be likely to respond – based on analysis of human immune system genes.

Eventually they whittled their selection down to just 14 epitopes which in different combinations could be the basis for two universal vaccines, covering 95% of known US flu strains and at least 88% of globally circulating strains, respectively. These were the results published in Bioinformatics in October 2016.*

The time seemed ripe for new collaborators, to turn this predicted vaccine into a real product. But since then, despite numerous presentations at conferences to 'wet' lab immunologists, the team has struggled to recruit suitable co-workers. They find there's a major barrier in research culture – making it hard to break into established circles.

"None of us is a lab worker, and we've had difficulty transitioning to the next stage of getting our theoretical prediction tested," says Gatherer, who began his career as a virologist but hung up his lab coat in 1995. "Although it attracted a lot of attention at the time and had a lot of hits on the Bioinformatics website, that doesn't necessarily translate into more mainstream scientific interest. We didn't get lab people approaching us saying 'we'd like to test your vaccine'".

Even the notion of a universal vaccine raises doubts. "Sometimes you hear a little groan coming up from the audiences. There have been a lot of false starts and false dawns in the past with universal vaccines that haven't quite worked... When they hear about a new universal vaccine project they're naturally a bit skeptical."

Tribal culture

The problem goes deeper, according to Gatherer. "The division which has grown up between computer biologists and lab biologists is still very much a tribal thing. There aren't that many people that cross over between the two. I think there's still a feeling... that lab biologists want bioinformaticists to do computational biology around their idea. The idea that a bioinformaticist would come into a lab and say, 'I've had a splendid idea and I think that you lab people should spend five years working on it meets with a bit of resistance."

Clearly, success in vaccine research requires not only vast sums of money but also partnerships across different disciplines. The lack of a collaborative infrastructure makes it harder for one team to get beyond the theoretical stage.

"There are many ways of turning an epitope into a vaccine candidate; they all have to be made and tested in mice, at least," says Adrian Hill, Director of the Jenner Institute at the University of Oxford. "No company is going to look at anything until you've done expression of a protein, put it into a scaffold, found an adjuvant, immunised animals, looked at immune responses, to see does it really work in the mouse. Then you're beginning to get close to a paper that you can publish as a vaccine candidate."

And the next steps - financing the manufacture of the vaccine candidate for human safety and efficacy trials in multiple locations and settings - can take 10 years or more, and require very distinct expertise. "You need microbiologists, molecular and structural biologists, immunologists, clinical triallists and manufacturing people. You can't do this on your own and you have to make sure these skill sets are all aligned and working together otherwise nothing goes forward," says Hill.

Hill is co-founder of Vaccitech, a new company which has a prototype universal flu vaccine in phase 2 efficacy trials in elderly people. The vaccine was first tested in small-scale human trials in 2007, but its development stalled without further investment. With £10million from venture capital, Vaccitech formed in May 2016 to put this design through further human clinical trials, and develop other types of vaccines.

Other candidate 'universal flu vaccines' are in earlier stages of development – for example by Emergex, another Oxford-based company.

In contrast, bionformaticists working in isolation may find it increasingly difficult even to publish new computational predictions. "The question is, where do you go next?" asks Gatherer. "We can do more prediction, or do better prediction, but we're always going to have the question asked, where is your laboratory proof of principle on this?"

Taking the lead with Ebola

Other efforts to curb newly emerging diseases offer more grounds for optimism that needed collaborations can be conjured up.

For example, bioinformaticists found themselves at the heart of an international response to the deadly Ebola outbreaks in West Africa. Ebola broke out first in the mid-90s and again in 2014 in Guinea, infecting more than 28,000 people, and killing over 11,000.

Bioinformaticists worked closely with field biologists to sequence biological samples from around 10% of affected patients, and tracked the evolution and spread of different Ebola virus strains. They demonstrated its spread from Guinea to Liberia, to Sierra Leone and back to Guinea, providing new insights into the virus's pattern of spread, and helping plan measures of containment.

"That was a good example of theoretical biologists taking the lead. The lab people were very willing to cooperate because they saw the bioinformatics made a difference. But there are still lab biologists who might say that's the tail wagging the dog, and they would like it to be the dog wagging the tail," says Gatherer.

However, when it comes to Ebola vaccines, developers have gone back to work from two decades ago or longer, including projects by US defense researchers who explored the option of vaccines to protect against possible bioterrorist attacks. One candidate was created in 2003 by the Public Health Agency of Canada but was left on the shelf for lack of interest. Only following the outbreak of 2014 was there demand for a vaccine. Astonishingly, with backing from Merck, the vaccine went

* Sheikh QM, Gatherer D, Reche PA and Flower DR. Towards the knowledge-based design of universal influenza epitope ensemble vaccines . Bioinformatics 2016;32(21):3233–9

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from first testing to large-scale proof of efficacy in less than a year. The vaccine is still not yet fully licensed, but following the new outbreak in April 2018 in DRC, it has been given on the basis of 'compassionate use' to all contacts of those who have contracted Ebola, as well as health workers and any other frontline staff.

Other candidate Ebola vaccines are now also being developed, including by GSK and Janssen Pharmaceuticals.

Being prepared

The Ebola experience has also highlighted a more recent collaborative culture among funders. In 2017, the Coalition for Epidemic Preparedness Innovations (CEPI) formed, government and philanthropic partners including the Bill & Melinda Gates Foundation and Wellcome Trust. The idea was to fund development of vaccines against so-called neglected diseases, including MERS, SARS, West Nile virus, NIPA and Dengue. With nearly $500million raised so far, CEPI is supporting efforts at epidemic preparedness, by developing vaccines that can be stockpiled until needed.

Another recent trend is a shift in academia towards building translational capacity, enabling researchers to take the products of basic research and apply them to health care. Many UK institutions, including Imperial College London, are setting up new translational research facilities, with support from the UK government's Developmental Pathway Funding Scheme, Innovate UK, Wellcome Trust and the Health Foundation.

A new culture of realism

The rapid progress around an Ebola vaccine owed part of its success to the relative simplicity of the Ebola virus. In contrast, organisms such as the malaria parasites, with its multiple stages in human and mosquito hosts, present a more difficult challenge to vaccine developers. The flu virus is somewhere between the two, according to Hill.

Hill started in malaria vaccine development more than 20 years ago, and has witnessed a change to a more realistic attitude in the malaria vaccine field. There is still no really effective vaccine that provides lasting protection against malaria. The challenge is partly technological – due to its complex life cycle – and partly financial – given the likely low profit margin on vaccines that are mainly needed in the poorer parts of the world.

"There's a joke in the malaria field that everyone would say 'Yeah, [the vaccine] is coming in five years.' It became such a joke that Princess Anne, who was very active in supporting tropical medicine at the time, would come up and say to people like me, 'I suppose the vaccine's five years away?'"

"The reason was that most people working in a university hadn't got the foggiest idea of what it takes to go from a vaccine candidate that really is going to work to get it licensed and deployed. The reality is that if you're not in your phase 3 trial, or about to start it, you are more than five years away from having a vaccine licensed."

The experiences of bioinformaticists Darren Flower and Derek Gatherer, and biologists like Adrian Hill, provide a glimpse into some of the challenges surrounding vaccine research, and the concerted effort needed. It also points to a character trait that no doubt Princess Anne saw in those whom she met, an aspect of research culture that has not changed for decades – the need to persevere, despite the barriers.

Cold war, hot science

By Rebecca Mileham

Cooperation between scientists in different countries can be thwarted by political conflicts or security concerns. Sometimes, though, science still finds a way, as the determined quest for superheavy elements shows.

The journey north from Moscow to the Joint Institute for Nuclear Research (JINR) takes two hours. Along the way there is the odd glimpse of a gold-domed Russian Orthodox Church, a lot of road construction activity, and then miles of peaceful forest. Every now and then, at the tree line, you pass a stall selling home-made produce – jars of jam and pickle, woodland berries and mushrooms.

"There was once nothing here besides the river and the forest," explains 85-year-old Yuri Oganessian upon my arrival in Dubna, the town that has grown up around JINR. "The institution was founded in 1956 and today there are 1200 scientists working here from around the world." Oganessian has been part of what is now named the Flerov Laboratory of Nuclear Reactions since its beginnings in 1957, first under Georgy Flerov, its founder, then as director himself, and today as scientific leader.

Over those six decades he has been a key figure in exploring some of the most fundamental scientific questions – How many chemical elements are there? How can we make elements with heavier nuclei? And will some prove to be stable and long-lived?

Oganessian is currently the only living person to have an element named after him. It is number 118, which neatly completes the seventh row in the periodic table and is called oganesson. The accolade, bestowed in 2016, came with the blessing of both Russian and American colleagues who had worked together on element 118's creation through experiments done at JINR.

But agreeing on the existence of new elements, along with their names, has not always been a walk in the park. In the Cold War years, American and Russian scientists competed to create elements with atomic numbers greater than uranium, the heaviest naturally occurring element. Tempers, careers and reputations rose and fell with the discovery, confirmation and naming of new substances in the periodic table.

The scramble for priority continued until 1989, then things changed. A collaboration began between the team at the Flerov Laboratory in Dubna, and an American team working at Lawrence Livermore National Laboratory (LLNL) in California. And that partnership yielded the discovery of the superheavy elements 114 and 116 by 1998, and the confirmation of elements 113, 115, 117 and 118 in the next 20 years.

So how and why did collaboration eventually prevail over competition? Did a changing political climate in the Soviet Union thaw scientific relations? Who brokered a conversation and when? Did leadership styles or team dynamics help overcome institutional and political barriers? And if the partnership had never begun, would we still be looking at a periodic table with gaps?

The nucleus: heart of the matter

"I would say it was scientific motivation that enabled the formation of the collaboration – we were interested in the same science, and continue to be so today," says Mark Stoyer, who now leads the Experimental Nuclear Physics Group at LLNL. He joined the American team in 1998, and says the search for new elements was actually a secondary concern. "It was the desire to understand very heavy nuclei at a more fundamental level. In order to understand the interactions of neutrons and protons with each other in a nucleus, and why a nucleus stays bound together, it is important to study a wide range of nuclei from very light to very heavy systems."

The nucleus gives an atom its identity. Hydrogen is element number one. It sits at the top left of the periodic table, the simplest atom with a single positively charged proton at its heart, and a single negatively charged electron orbiting around. Next is helium. It has two protons in its nucleus – giving it an atomic number of two and defining it as helium – plus two neutrons. In orbit are two electrons.

It seems simple – and in many ways it is. As the number of protons in the nucleus increases, you move through lithium (3), beryllium, (4) boron (5) and get to carbon (6). If you keep going, you'll arrive at glowing neon (10), semi-conducting silicon (14), precious silver (47), slippery mercury (80) and radioactive polonium (84). Each has an extra proton in a nucleus of increasing mass – along with extra neutrons and orbiting electrons – and all are part of a natural pattern.

But move to the lower right-hand corner of the periodic table, beyond uranium (92), and the elements no longer exist in nature. At the University of California, Berkeley, during the 1940s and 50s, scientists bombarded different samples of metals using a particle accelerator, producing neptunium (93), plutonium (94), americium (95), curium (96), berkelium (97), californium (98), and mendelevium (101). They also discovered einsteinium (99), and fermium (100) in the fallout from hydrogen bomb explosions. The team included the pioneering chemist Glenn Seaborg, and physicist Edwin McMillan, who shared the Nobel Prize for Chemistry. Nobelium (102) proved more controversial. A group in Stockholm announced its discovery in 1957 but couldn't confirm the feat. Seaborg's group claimed discovery by a different method. The Russian team led by Georgy Flerov came onto the heavy element scene, disputed the American finding, and claimed its discovery themselves.

More disputes followed. During the 1960s and 70s both Russia and America announced they had found what would eventually be dubbed lawrencium (103), rutherfordium (104), dubnium (105) and seaborgium (106). Priority took many years to untangle, in a chilly Cold War atmosphere between the two superpowers. During the early 1980s, another player entered the game. Scientists at the GSI Helmholtz Centre for Heavy Ion Research in Darmstadt, Germany, added bohrium (107), meitnerium (108) and hassium (109) to the roster. Chemistry journalist

Kit Chapman, who has a particular interest in the superheavy elements comments, “It’s all or nothing. If you discover an element you are immortalised forever. There is no coming second.”

Yet despite the competition, scientific conversations did continue. “In science, collaboration has existed since the Middle Ages,” says Oganessian, in excellent English. “If I make a discovery, my collaborator will take it into account in his experiment. There are also mistakes to take into account.”

“I attended a seminar in which a Russian delegation was visiting and sharing their research,” recalls Mark Stoyer of the mid-1980s. “The delegation had 3 or 4 members – including Flerov and Oganessian, I believe. The seminar was delivered in Russian, for accuracy, and then translated to English. I remember it vividly because it was a long, slow process for the speaker to say a few things, get it interpreted, then the folks in the audience to ask clarifying questions, have that interpreted, and so on.”

It’s a reminder that despite prevailing difficulties, a common scientific interest still helped bind the parties together.

Cold war thaw

It is no surprise that post-war research into heavy elements should first have emerged in the two nations who completed atomic bomb projects. Expertise in handling radioactive uranium and plutonium gave both a head start. There was also the remarkable parallel experiences of the teams’ leaders.

Georgy Flerov served in the Russian air force during the Second World War. He noticed that work on nuclear fission had ceased to appear in American, British and German journals – and deduced that it had become classified research as the different powers worked towards atomic weapons. As the result of a letter Flerov wrote to Stalin in 1942, the Soviet bomb project began.

Meanwhile in the United States, Glenn Seaborg’s discovery of plutonium, with its fission chain reaction, fed into the Manhattan Project and the atomic bomb dropped by the Allies on Nagasaki in 1945.

“These two men, Seaborg and Flerov, were more or less the same age,” comments Oganessian. “When they were young, Seaborg discovered plutonium and Flerov discovered spontaneous fission. When the war started, both were involved in atomic bomb projects in their own countries.” After the war, they built their own research teams, working separately in Dubna and at the University of California, Berkeley. “But what is interesting is that with all the discoveries made, sometimes the difference was only a few months,” he added. Russian researchers would publish in Soviet journals, while others’ work appeared in the international press. They were two different worlds.

Work on building the particle accelerators required heavy ion science. Seaborg had used a 150cm cyclotron to synthesise elemental discoveries. At JINR, Flerov constructed a 300cm heavy ion cyclotron. These machines had been invented in the 1930s at Berkeley, and used magnetic fields to whirl charged particles to enormous speeds.

Andrey Popeko, deputy director of the Flerov Laboratory, explains the cyclotrons’ role: “At the start of the 1950s, a method of amalgamation of heavy nuclei was devised simultaneously, here and at Berkeley.” By smashing two kinds of atoms together, you could fuse their nuclei to make a heavier one. In this way, a cyclotron lets you produce fermium (100) from uranium (92) by amalgamating it with oxygen (8), creating a nucleus with 100 protons. Andrey goes on, “Both nuclei are positively charged, so they repel each other. You have to accelerate them at the correct energy so the nuclei fuse and don’t disintegrate.”

Seaborg and his team had discovered elements 94 to 101. The goal of the Flerov lab, when it began its work in earnest in 1956, was to start by making element 102. As the atomic number went up, however, the chance of making the nucleus decreased, while the requirement for more intense accelerator beams increased. It was definitely tricky science.

By the 1980s the need for more resources was clear in both countries. Mark Stoyer says: “Experiments in the superheavy element region were getting much more difficult and resource-intensive in terms of time, money and materials. The LLNL heavy element group was having difficulty obtaining beam time for experiments at the Lawrence Berkeley Laboratory (LBL) cyclotron. LBL had 3 or 4 groups demanding beam time for their research, so the chances of getting even several weeks of time was minimal. In addition, the LBL heavy element group was interested in different kinds of experiments.”

Financial restrictions were also biting during the last years of the Soviet Union, when investment faltered. Mikhail Itkis, another former director of the Flerov Lab explained: “When the Soviet Union collapsed there were difficult times. We didn’t have money to buy good detectors and so on. People supported us in principle, but our budget was very poor at that time.”

Despite these issues, the Flerov lab was still a major player in the search for new elements. And as Mikhail Itkis explains, specialism helped lay the groundwork for collaboration. “We have the best accelerator around the world in this field. It’s not high energy, it’s not very low energy for ions, it occupies a special place.”

LLNL at the time had particularly advanced electronics for analysis, while Oak Ridge National Laboratory in Tennessee had good material for the targets used in experiments. It was the basis for a collaboration that continues today. “Each group has success in different areas - so when they come together, there is success, because they are the first in their fields,” says Itkis.

“The first visits to Dubna to perform experiments were to the Soviet Union,” says Mark Stoyer – but times were changing. The Berlin Wall fell in November 1989, and the Soviet Union collapsed in December 1991. “The scientific collaboration started and later flourished during this politically unstable time,” he adds. Team members Ken Moody and Ron Lougheed were in Dubna when Georgy Flerov died in November 1990. By this time Yuri Oganessian was the lab’s director.

Deeper layers

The breakthrough in the search for superheavy elements was first a theoretical one. In the early part of the 20th century, theoretical physicists worked on the basis that the nucleus of an atom behaved like a drop of liquid, becoming more unstable as the charge increased and disintegrating through the process called nuclear fission.

"The general conclusion for the liquid drop model was that elements higher than uranium may not exist," explains Oganessian. "This was the limit – and my work started from this limit in 1955. Everybody accepted it and we called it the classical theory of fission. But it was not correct."

A spanner in the works of the classical theory was that two apparently identical nuclei may decay with different probabilities. Researchers eventually concluded that there were different states in which the nucleus could exist, known as the ground state and the isomeric state. "If you find such a phenomenon that seems to contradict the liquid drop model, this is like Pandora's Box, you know, it's opened and then there are so many questions. You come to the new unknown vault and now you have to work to understand it," says Oganessian.

The idea that the orbiting electrons can exist in a number of energy levels had been known for decades. But within the nucleus itself, scientists realised, there is also structure. Particular numbers of protons and neutrons, corresponding to full shells, are especially stable. In 1949 Maria Goeppert Mayer and Hans Jensen developed this model and later shared the Nobel Prize in Physics.

Glenn Seaborg took this idea further in the late 1960s, predicting that among the superheavy elements there would be what he called an "island of stability" that would make some elements longer-lived than expected. Element 114, for example, should be particularly long-lived if scientists could make atoms with a total of 298 neutrons and protons in their nucleus.

Fascinatingly, Georgy Flerov had also proposed such an idea in 1957 in front of a key Soviet scientific council. Andrey Popeko explains: "Flerov had a very surprising sense of intuition. He could predict many things without detailed study. In 1957, when invited to explain the laboratory's future work, he presented ten proposals. Among them was the superheavy elements and he explained that somewhere in this region there must be – although he did not call it this at the time – an island of increased stability."

But to create elements on the way to 114 a new scientific technique was needed, which Oganessian pioneered in the 1970s. "Element 106 you may produce from californium and oxygen or by taking lead and using chromium," says Oganessian – reactions in which a light element is fired at a heavier one. "But after that I proposed a new reaction, called cold fusion." In this kind of reaction, the two nuclei to be fused together are much closer together on the periodic table, more similar in size. Teams in the US, Russia, Germany and Japan were now all on the experimental trail. Different groups eventually used the cold fusion reaction to create elements 107 to 113 in minuscule amounts.

Even this method, however, met its match. Oganessian recalls: "To produce three atoms of element 113, it took our colleague Kosuke Morita nine years overall, Japanese. So this is one reason why you come to the end of the cold fusion method. It is not practical."

Oganessian's new method, which would eventually take the discoveries right up to element 118, was hot fusion. Kit Chapman explains: "In hot fusion, you smash together light projectile nuclei and heavy target nuclei to create a new nucleus. The problem is that the nucleus has a lot of energy and it wants to blow up." To avoid this, you use a projectile beam of calcium-48 atoms which have the usual 20 protons in their nucleus, but 28 neutrons. "The beam is very neutron-rich," says Chapman. "It has 8 extra neutrons which it discharges like ballast, relaxing the state of the nucleus so that it remains stable."

Brokering a collaboration

So how did the US-Russia collaboration begin? Mark Stoyer's understanding is that the collaboration was brokered by Ken Hulet – who had worked with Glenn Seaborg at Berkeley, and was by now a senior member of the LLNL team – in conjunction with Georgy Flerov from Dubna. The two met in 1989 at one of the regular round of international conferences, and agreed to work together. "This was remarkable at the time," Stoyer comments. "One of the US nuclear weapon labs and one of the Russian nuclear science labs collaborating – during the Cold War."

Yuri Oganessian plots a slightly different route into the partnership. He met with Glenn Seaborg to discuss working together on creating atoms of element 106 with particularly high numbers of neutrons in their nuclei. His idea was that this could lead to creating element 114 in a longer-lived, more stable state.

Seaborg was a generation older than Oganessian and they had what the latter describes as a 'perfect' relationship. Yet despite the mutual respect, Seaborg did not take up the opportunity – rather it was Oganessian's contemporary Ken Hulet who agreed to collaborate.

According to another report of the collaboration's genesis, Ken Hulet made contact with Dubna and agreed a mutually beneficial sharing of resources in terms of detector technology and accelerator capacity. A further account has Oganessian persuading LLNL physicists to share rare kinds of calcium and plutonium for a joint experiment to make element 114.

However the agreement was reached, the collaboration flourished. For his part, Oganessian recalls, "When I became director [of the Flerov Laboratory], I wanted to change the relationship between the two groups that were working for many years on the superheavy elements. 1989 was the beginning of Gorbachev time. I guess my vision was quite naive, but I felt, now, I have to try."

By late 1998, the two groups were preparing to try to make element 114 using a plutonium target and the beam of calcium-48. "The reaction had been tried before but the Dubna/LLNL collaboration had improved the apparatus enough to have much higher sensitivity. All of this improved the quality of the results that then came from the collaboration and fueled its future success," explained Mark Stoyer, who joined the group at this point. His wife, Nancy Stoyer, was already on the project.

"The experiment would take 3-4 months, so we divided into two teams to visit Dubna a month apart," he recalls. No one expected any big outcome at this point, "but amazingly, the first event occurred between our visits," he says. The partners had successfully produced element 114, and they would soon do the same with element 116.

Leadership and team culture

Further successes followed with elements 115, 117 and 118 – indeed, the Russia-US partnership has been very successful for nearly 30 years, and has its face firmly set to the future. Sergey Dmitriev, the current director of the Flerov Laboratory, will unveil a new accelerator in the next few months. "It is called the superheavy element factory," he says. "The projectile beam of this cyclotron will be at least ten times more intense than we have today. So we can start the synthesis of elements 119 and 120."

Plans are to make element 119 by using a berkelium (97) target plus a neutron-rich titanium (22) projectile, which has 50 protons and neutrons in its nucleus. In the case of element 120 the target will be made from californium (98). In addition, "We also have a big program to study the chemical properties of the new elements," says Dmitriev. Such short lifetimes don't give much time to study these elements – but he is confident it's enough.

The work will still be firmly collaborative. "Several factors are important in sustaining the collaboration," says Mark Stoyer: "Continued interest and passion in the science, strong working relationships we have developed, and mutual respect. The successes of the past naturally lead to new questions and directions in the field – and we remarkably shared a common vision for the scientific path forward during this time."

"Several factors are important in sustaining the collaboration, continued interest and passion in the science, strong working relationships we have developed, and mutual respect"

Mark Stoyer

Yuri Oganessian doesn't mind calling the collaboration idealistic. "We come together and say, 'you've got this, we've got that'. Nothing is guaranteed, but all the people who are with you understand. We are all trying together – there is a kind of connectivity that I like very much. The principle is that you contribute as much as you can."

The cultures of the two groups are significantly different, Stoyer says. "There is a stronger hierarchy in Russia and team members are more focused on their particular task. In the US, all members of the team analyse the data depending on their interest in a particular experiment. In Russia the analysis of the data is performed by a single specialist. The cultures of Russia and the US are very different. In Russia, if it is not strictly allowed, then it is assumed to be forbidden. In the US, if it isn't strictly forbidden, then it is assumed to be allowed."

The trust between the partners has been carefully built, however. Mikhail Itkis explains: "It's very important that in each discovery of a new element, the experimental decay chain is simultaneously analysed in Dubna and in Livermore. Independently. And then after that we compare, and publish."

Face-to-face meetings are good, reports Oganessian, but online links are crucial. "We have a connection so that every day everyone can see what has happened here."

Stoyer agrees, "We had a dynamic of vigorous discussion about the interpretation of the data and results from day one. Nothing was ever published without a consensus. We always wanted to produce the highest quality results and valued the working environment that embraced new ideas and their open exchange and critique."

Without the collaboration, both sides agree the discoveries of the heaviest elements could not have been achieved. Oganessian says, "I would say for sure, without the collaboration, we ourselves here would not have been able to make these elements. The teams in Livermore and Oak Ridge also could not make the elements. There were many barriers, not only political, so we had to ask ourselves, is there a way of combining into a joint group?"

On the two sides of the collaboration, leadership has been handled differently. "Group leadership at LLNL has rotated more than at Dubna and technical leadership has changed more often in the US as well," explains Stoyer.

But while all have contributed to the collaboration's success, perhaps Yuri Oganessian gives us a good model of what it takes to pursue this esoteric yet intriguing and appealing branch of science, year after year, in the town built on the banks of the Volga.

As Kit Chapman explains, "Oganessian is really the glue in the whole collaboration. He is the driving force – the diplomat that such a project needs. He is a more successful and modern leader than Flerov was, with a collaborative spirit. He is the guy that found the path, who made a way to do what they needed to do."

From collective investigation to citizen science

By Sally Shuttleworth and Chris Lintott

We normally think of collaboration between accredited scientists. But there is a long history of research that involves lay observers. Contemporary large-scale projects abound that build on and develop this tradition, incorporating vital contributions from members of the public.

Science is not always done in the lab. Over the last decade 'citizen science' has opened up the possibilities of large-scale participation by volunteers in science, online, at home, or in the field. Zooniverse is the world's largest online citizen science network with 1.6m participants. It promotes 'people-powered research', and offers the promise of taking part in 'real cutting edge research'. It feels like a revolutionary moment. Indeed the US government, under President Obama, recognised the possibilities, and supported federal agencies to set up citizen science schemes. One such programme was named in 2016 as one of the top initiatives in expanding the US capacity in science, technology and innovation, with the award citation noting an estimate that 'in kind contributions of more than a million citizen-science volunteers to biodiversity research alone have had an economic value of up to $2.5 billion per year'.

Dollar value aside, the award is striking for its vision of future science as a large-scale collaborative activity, breaking down the borders between professional and 'citizen' science. Yet, whilst the numbers involved are new, the impulse is not. One can track the roots of current initiatives before the full professionalisation of science in the early twentieth century.

Historical examples abound. Charles Darwin maintained a network of over 2000 correspondents, drawing for example on the expertise of cattle breeders and pigeon fanciers, or local naturalists. He wrote to gardening and natural history magazines, asking readers for information on topics as varied as the feet of otter hounds, or a breed of mouse-coloured ponies. In effect he was running his own, highly labour intensive, citizen science network, drawing a wide variety of data from experts in diverse fields.

Darwin built on the teachings of his 'dear old master in Natural History', John Henslow, Professor of Botany at Cambridge, who instructed university students and working-class school children alike in the power of botany to extend both the observational and reasoning faculties.

The nineteenth century saw local natural history and field clubs set up from the 1830s onwards across Britain. Many still continue today. Their detailed, often unbroken, records provide invaluable data for the Biological Records Centre of the Botanical Society of Britain and Ireland (founded in 1836). Their meticulous maps of the flora of each region over time contribute to current research on both conservation and climate change. Even as university science departments have grown, detailed knowledge of local flora has remained firmly in amateur hands. Indeed, as early as the 1890s there were complaints that the modern biological student had become too specialised. He had been tempted away from the hedgerow and sea shore and into the laboratory: 'He knows the structure of a certain number of "types," but he walks as a stranger among the living animals and plants that surround him', his understanding of the organism reduced to a 'complicated collection of tissues… spread out into a panorama of thin slices'. Raphael Meldola, Professor of Chemistry at UCL, and author of this piece in Nature (June 4, 1896), called for an end to such specialisation and for the 'scientific energies' of local societies to be used to create centres of 'intellectual enlightenment' for the country. Then as now there was a huge sense of scientific potential, if the nets of scientific activity could be widened.

Natural history in the nineteenth century is sometimes seen as the province of interested clergy or other educated gentlemen (on the model of George Eliot's Reverend Farebrother in Middlemarch, with his drawers of beetles). Research by Anne Secord and others, however, has corrected this view. As another article in Nature noted in 1870, 'Were statistics obtainable, it would surprise outsiders to learn how large a proportion of the practical observations in Astronomy, Geology, or Natural History' were made by working-class townsfolk. Local natural history societies varied in their social mix but they all offered the possibilities of intellectual exchange and collective endeavour, with many publishing their own periodicals. For all involved there was a strong sense of mission, a belief, as a member of the Wiltshire Archaeological and Natural History Society put it in 1854, in the power of collective work: 'to try what union of industry, and union of accomplishments may do; to collect the scattered elements of strength, and to set several to work instead of one'.

Attempts to draw together participants in scientific observations date back still earlier. Edmund Halley, for example, records in the Philosophical Transactions of the Royal Society of 1714 how he prepared for a total eclipse of the sun in April 1713 by creating a map of England describing its track which he 'dispersed all over the Kingdom, with a request to the curious to observe what they could about it'. All you needed was a pendulum clock. His article draws together the findings of the 'curious', together with his own observations at the Royal Society, duly noting the names and locations of all his participants. On a far grander scale, William Whewell, researching tides in the 1830s, organised an analysis of tidal patterns between 8-28 June 1835 at hundreds of coastal stations on both sides of the Atlantic, in Britain, Europe and America. He pursued this work until 1850, extending his network worldwide, and publishing a series of 14 studies in the Philosophical Transactions.

Whewell's model was rather top-down, designed to extract information, rather than foster scientific participation and communal exchange. There were, however, attempts at this period to create more

These examples show Victorian networks operating on a large scale, and with an idealistic vision of mass collaboration in the development of science, anticipating contemporary citizen science

Sally Shuttleworth and Chris Lintott

democratic networks of scientific observers, the most successful probably being that of the meteorologist G. J. Symons. Starting in 1860, Symons set out to recruit a nationwide cohort of volunteer observers, who were required to take rainfall readings without fail. He quickly signed up 500, and grew the network to 3,400 by the time of his death in 1900, publishing annually a detailed report and tables giving the year's results. His energy in creating this network was extraordinary; he travelled throughout Britain visiting his 'staff' of observers. He personally wrote to 1400 newspapers, calling both for historic records of rainfall and new observers, stressing, as in a letter in the Times of 1863, that the activity was open to all: gauges could be sent to those who could not afford them, and 'neither is there any difficulty in observing, for my correspondents are of both sexes, all ages, and all classes'. It is a wonderfully inclusive initiative.

In 1866 he set up Symons's Monthly Meteorological Magazine to offer a forum for exchange and discussion for his observers; the magazine continued after his death, and was eventually taken over by the Meteorological Office in 1920, only ceasing publication in 1993. Ironically, Symons had fiercely maintained the independence of his network during his lifetime, fighting off attempts by the Met Office to take over, arguing that such a move would extinguish the observers' 'esprit de corps', and 'would be at the cost of that intelligent independence of thought which so greatly rules the progress of science'.

In a preface to British Rainfall in 1880, he reflected on why his staff of voluntary observers, who included, he noted, 'all classes from peer to peasant', daily gave up their time and energies with such willingness: 'Minor motives may have some influence, but I believe that the leading sentiment which binds together British Rainfall observers is the consciousness that they are helping gradually to store up a mass of information which is, and will yearly become increasingly, valuable to the nation at large in relation alike to Agriculture, Sanitation, and the proper appropriation of the water supply of the British Isles.' The vision is future-oriented, looking beyond daily detail to some of the most pressing social problems in an increasingly urbanised society. As with the botanical records, the long-run observations, captured in the annual surveys of British Rainfall and now available digitally on the Met Office website, take on new salience in an era of climate change.

Another large scale network was that of Eleanor Ormerod (1828-1901), who from 1877 until her death in 1901 produced an annual report, based on volunteer contributor returns, on 'Injurious Insects', or 'common farm pests'. She had originally responded to a request from the Royal Horticultural Society, in the Gardeners' Chronicle of 1868, for readers to send in specimens of vegetables attacked by insects. Her first 'network' consisted of the labourers and children on her father's estate but she subsequently branched out, working with farmers, market gardeners, and school children in her mission to bring better understanding of entomology to farming.

Although barred by her sex from membership of most learned societies (apart from the Meteorological Society who made her their first female fellow), she became honorary entomological adviser to the Royal Agricultural Society, and a leading international expert, advising on insects, for example, in South Africa, New Zealand and China. She was a member of Symons' Rainfall Observers (contributing 12 years of unbroken records), and was no doubt inspired by his example. Like Symons she was anxious to ensure that all her contributors were named and given 'the fullest recognition possible'. This extended to her work with schools, with her youthful contributors' specimens all acknowledged by name in her displays, so that, as she wrote to one contributing school, 'your scholars have a world-wide name'.

Together, these examples show Victorian networks operating on a large scale, and with an idealistic vision of mass collaboration in the development of science, anticipating contemporary citizen science, made possible by the internet. Indeed, some of the largest projects carry on the very same work that was being done back in the 19th century; eBird, a project of the Cornell Laboratory of Ornithology, invites birdwatchers from around the world to record their sightings. Their collective contributions are of great use to scientists, but there is an element of individual pride here too as volunteers use the site to keep track of what they've seen and to compete for rank amongst enthusiasts in their area.

Other, less traditional, observational projects are also enabled by modern technology. The iNaturalist phone app, allows identification of pretty much any species whose photo can be uploaded. Artificial intelligence deals with the most common examples, but the power of iNaturalist is the online community of amateur experts, keen to identify even the most obscure species.

The appeal of the app is that moment when the unusual caterpillar or strange leaf in front of you gains a name, although it is hoped that the vast database of sightings, each geotagged with a location, will also fuel scientific discoveries. It is easy to find projects, however, where the intrinsic goal of contributing to science is the primary motivator.

Take Galaxy Zoo, for example, which inspired the development of the Zooniverse platform. It opened in 2007, inviting volunteers to record the shapes of galaxies - the morphology, or shape, of a galaxy records its dynamical history, and is sensitive to past mergers and encounters with other galaxies. It was expected to appeal primarily to amateur astronomers but reached a much wider collection of observers, including many who had not previously been interested in astronomy. The result was a collection of hundreds of thousands of galaxy labels within a few days of launch.

The scientific results have been plentiful, and surprising. Just as amateur naturalists were thought to know their patch of the world and the organisms within it better than professional scientists, so some Galaxy Zoo volunteers have made serendipitous discoveries of objects which would otherwise have been ignored by professional astronomers. The most famous of these is Hanny's Voorwerp, an immense glowing gas cloud named for its discoverer, Dutch schoolteacher Hanny van Arkel. There are plenty more.

They include the 'Green Peas' – small, round galaxies visible in the background of images that volunteers

were asked to classify - which turn out to be the most efficient star factories in the local Universe. Located in the least dense parts of the Universe, these systems are giving astronomers clues as to what galaxies in denser environments must have been like billions of years ago. So many unusual objects have been found that the Hubble Space Telescope is currently collecting high-resolution images of a host of unusual systems logged by Galaxy Zoo, from distorted disks to galaxies whose outer regions glitter with enormous rings of new stars.

More than a hundred peer-reviewed papers have used Galaxy Zoo results. The project is clearly contributing to science, but are the individual volunteers actually doing science when logging on and classifying galaxies? A common criticism of projects such as Galaxy Zoo is that the 'citizen scientists' are mere cogs in the machine, whose labour contributes to science but who are not meaningfully involved.

This recalls the debate about ownership of the rainfall monitoring network more than a century earlier. It is clear from the discussion boards that accompany the project that at least some of the participants in Galaxy Zoo feel as strong a sense of ownership over 'their' project as their predecessors did, and that this is something that develops over time.

Research carried out by the Zooniverse team working with social scientists has shown that, unlike citizen science projects that match pre-existing interests (as in eBird) volunteers become motivated to find out more about the subject with which they're engaged. Rather than appealing only to amateur astronomers, Galaxy Zoo finds a large community of people who are then inspired to seek out information about astrophysics, learning more than the site itself can teach them.

It is tempting to start thinking in terms of citizen science careers, so that people progress from classification, through discussion and on to more 'advanced' scientific work. Good examples include projects such as Planet Hunters, another Zooniverse effort which asked volunteers to consider data from NASA's Kepler space telescope. Kepler was built to find exoplanets – orbiting stars other than the Sun – by monitoring nearly 150,000 stars, watching for the dips in brightness that reveal the presence of a transiting planet.

Detecting these transits is often a task for specialised software, but such programmes can be confused by noise, and by variations in the brightness of the host star itself. Stars can have starspots, just as the Sun has sunspots, and these can mimic the effect of transits. Planet Hunters volunteers have found nearly 100 new candidate planets, including a host of transits that might indicate the presence of planets on long-period orbits, the equivalents of Jupiter or Saturn in our own Solar System.

They have also found the unexpected, including a world now known as Planet Hunters 1b, the only known planet in a four star system, in orbit around a pair of stars which is itself gravitationally bound to another double star. The most remarkable find, though, was not a planetary system, but a misbehaving star. Now known as Boyajian's Star after the researcher who led the paper announcing the discovery, this otherwise unremarkable star displayed a pattern of rapid fading and recovery which has not been seen before.

It was identified first by a group of Planet Hunters volunteers, one of who – Darryl LaCourse – developed his own model for what might be causing the star to flicker so dramatically. His idea, of a transiting dusty disk, was sensible but later ruled out by infrared observations. The star attracted worldwide attention when a group of professional astronomers proposed the presence of an alien 'megastructure' as an explanation for the observed behaviour; subsequent monitoring of the star has now ruled this out, revealing that the degree to which the star dims in each dip depends on colour, ruling out any sort of solid obstruction whether natural or constructed.

This story of Boyajian's Star has been reported in blogs and email newsletters that keep the community of Planet Hunters (and those who participated in a later crowdfunding campaign which supports ongoing monitoring of the star) up to date. And more than thirty peer reviewed papers now report observations or offer explanations. This professional conversation remains separate from the volunteer dialogue; though two short papers have been published by citizen scientists in the new 'Research Notes of the American Astronomical Society' publication, these are not peer reviewed.

This highlights one of the challenges for citizen science projects which aim to provide opportunities beyond the kind of engagement the basic Galaxy Zoo or Planet Hunters interfaces provide. Writing a paper for a scientific journal is something that PhD students take time to learn, and is time-consuming. Even reading such a paper can be challenging; technical language is not designed to be understood by outsiders. Although in fields such as astrophysics almost all published papers are free to view, there is little evidence that the discussion that takes place in a citizen science project is informed by the literature.

Changing that will require changes to scientific publication practice rather than being something that citizen science projects can attack on their own. What is clear is that this form of distributed data analysis is spreading; the Zooniverse alone hosts projects from fields as different as particle physics and ecology. The latter has seen an especially rich diversity of projects spring up, working with the data being obtained by networks of camera traps. Grids of cheap cameras can either take images on a regular schedule, or are triggered by motion or infrared sensors, and provide a way to monitor diverse animal populations in detail which would otherwise be impossible.

A good example is the Penguin Watch project, which asks volunteers to count penguins in images obtained from cameras across the Antarctic Peninsula. Such a simple task, combined with the enduring appeal of the penguin, has proved extremely popular. The aim is to monitor the health of populations of three species of penguins as they nest and breed, and to tease apart the response of the populations to external factors including tourism, fishing and climate change. With the recent expansion of marine protected areas in the Antarctic region, there is a chance for citizen scientists' findings to have real influence on policy.

Penguin Watch feels like a very different project to Galaxy Zoo. The task is more concrete, the subject literally more down to Earth. Yet from a scientist's point of view, the process is very similar. Success depends on combining contributions from many volunteers to create a quantified consensus result, which can then be mined for scientific insight. The spread of this form of citizen science has come about partly because researchers have developed and shared new methods for deriving this consensus

which can be applied in areas far beyond their original domains.

A recent Zooniverse project, the Planetary Response Network, uses the tools of citizen science in a humanitarian context. Exploiting the rapid satellite coverage provided by swarms of microsatellites, PRN is deployed to assist first responders working in disaster-hit areas where mapping is either inadequate or immediately rendered outdated. Recent uses of the system have included identifying settlements in areas affected by the Nepalese earthquake of 2015, and mapping damage done by the Caribbean storms in 2017.

The path from naturalists corresponding with Darwin to a web-based project which helps in the aftermath of natural disasters may seem long, but they are connected by a common legacy in citizen science. Indeed, a direct predecessor of the Planetary Response Network can be found in the Royal Society Committee on the major eruption of Krakatoa in 1883, which had dramatic effects on weather patterns worldwide. The committee was chaired by G. J. Symons, coordinator of the rainfall network. Using his usual appeals in newspapers for information, he collected a treasure trove of material from observers worldwide which led, amongst other things, to the first discovery of the jet streams, so important both to modern aviation and meteorologists' understandings of storm patterns.

In all these cases, old and new, knowledge available but distributed amongst a crowd is gathered, and by being combined provides the opportunity for discovery. With the amount of data available to anyone with an internet connection increasing rapidly, the opportunity for this sort of collective action will continue to grow, and the potential for further, innovative projects will increase. The patterns of collective investigation of the past will be reinvigorated in the citizen science projects of the future.

Further reading

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The mad sessions of Francis Crick and Sydney Brenner

By Matthew Cobb

All collaborations rely on conversation. Sometimes, that conversation reaches a pitch of scientific creativity that is attained only rarely. Such was the celebrated decades long interaction between two of the towering figures of molecular biology, Francis Crick and Sydney Brenner.

In January 1957, Sydney Brenner, a young molecular biologist from South Africa, arrived at the University of Cambridge. He went to the Cavendish Laboratory where he moved into Francis Crick's office; the two went on to share their working space for more than 20 years.

Their office produced one of the great scientific partnerships of the twentieth century, but this was a collaboration that was rather untypical. It rarely involved joint laboratory work. Instead, every day, except for when one of them was travelling, the pair would discuss intensely about anything that interested them. For Crick and Brenner, collaboration was essentially about exploring and clarifying ideas, on an incredibly wide range of topics.

Their discussions produced answers some of the most crucial issues that faced biology, including the nature of the genetic code, how protein synthesis works and choosing the next great scientific challenges once the genetic code had been cracked.

Both men clearly craved this kind of interaction - both pursued intense collaborations with other scientists, before, during and after these two decades of joint work. Crick endlessly worrying away at the structure of DNA, bouncing ideas off Jim Watson, was described in the pages of Watson's novelised account The Double Helix. Similarly, Brenner worked closely with François Jacob in Paris, and with Seymour Benzer in Caltech – in both cases, their correspondence reveals profound friendship, similar scientific interests and above all a shared sense of humour.

But the collaborative relationship between Crick and Brenner was different. Their interests were broader, their friendship was deeper and their way of working together more intense. Above all, in their shared office they talked endlessly – arguing, chatting, coming up with unlikely hypotheses, haggling over experimental details.

Most of those discussions are lost – they echoed in the rooms they shared over those two decades, then faded

away. But the nature of their collaboration can be seen in their scientific papers, and in letters, memoirs, oral accounts by colleagues, and contemporary descriptions and photographs. They yield a picture of how two extraordinary men inspired, guided and corrected each other during two of the most important decades in the history of biology.

Meeting over the double helix

Crick and Brenner first met in dramatic circumstances in April 1953, when Brenner was a PhD student at Oxford. Agog at the news that Watson and Crick had cracked the structure of DNA, Brenner and two colleagues drove over to Cambridge. They walked into a brick-lined room, and there was the model of the double helix, together with Watson and Crick. Brenner recalled:

“Francis was sitting there. This was the first time that I met him and of course he couldn’t stop talking. He just went on and on and on, and it was very inspiring you see... So that’s when I saw the DNA model for the first time, in the Cavendish... And in a flash you just knew that this was very fundamental. The curtain had been lifted and everything was now clear as to what to do.”

Brenner was instantly convinced that he needed to work on DNA, preferably at Cambridge. The following year, Brenner and Crick both attended the Woods Hole Marine Biology Laboratory summer school in Massachusetts. The two hit it off and within a year Crick had convinced his bosses at the Cavendish that they should recruit Brenner; the young South African was so keen to come he said he would “work in a cupboard”.

During this period, while Brenner was back in South Africa and Crick was in Cambridge, the pair began an intense correspondence that resumed sporadically over the next two decades whenever they were separated. Much of the correspondence still survives, and it gives us a good insight into how the pair interacted.

The letters are often terse, outlining new results from the lab, describing recent discussions with colleagues or asking pointed questions, both technical and fundamental. They reveal two minds that managed to focus both on the big picture issues their research was addressing, and on precise experimental detail.

It was not all work, however; the correspondence also contains more personal moments. For example, on 25 February 1965, Crick began writing a letter to Brenner from California, but broke off suddenly because his wife, Odile, had just walked through a glass door. The next day, after Odile had received 100 stitches, Crick took up his pen again and continued as before (“I’ve got very interested in the histology of the nervous system and may do some work on this”). When the two men were not able to discuss regularly, they felt this absence keenly. As Brenner wrote to Crick on 6 February 1964: “We all miss you very much here, it’s very quiet, but I love having your desk to spread over as well. Hurry back soon”.

While the correspondence is illuminating, it covers only a tiny part of the time Brenner and Crick worked together. The key to their collaboration was in their face-to-face meetings, their endless talking about science. They talked in Cambridge, first in the Cavendish Laboratory; then in a low prefabricated building in the courtyard of the Cavendish, which was paid for by the Medical Research Council and nicknamed, with succinct accuracy, The Hut; and finally in the swish new four-storey Laboratory of Molecular Biology, which opened in 1962.

What they discussed

To a research administrator, the output of these discussions might seem quite slight. In those 20 years, Crick and Brenner published only six articles together, most of which have been cited under 250 times; only one has really made an impact, with over 800 citations.

But the significance of their work together cannot be measured that way. Although both men were employed by the Medical Research Council, their approaches to research were slightly different, with Crick tending to focus on theoretical issues to do with the genetic code and gene function, while Brenner was forever fiddling about in the laboratory studying the genetics of viruses. Although they collaborated intensely, they did not always work together on the same project. Another reason the publication numbers do not reveal the depth of their collaboration is that, as was often the case at the time, the pair did not systematically sign each other’s articles. Authorship included those who had actively contributed to a paper, not anyone who had discussed the ideas in it. When we consider the wider range of material they published on, singly or with other people, but which we know they discussed, the result is a remarkable contribution to modern biology.

First, their discussions by letter and in person led to a highly influential lecture given by Crick in September 1957, entitled “On protein synthesis”. In this lecture – the printed version was partly the work of Brenner, as shown by the acknowledgements – Crick outlined one of the fundamental ideas in modern genetics, the ‘central dogma’. He hypothesised that once the genetic information present in DNA has been turned into a protein, through the intervention of RNA, it cannot get back into the DNA sequence. Thus our genomes cannot be rewritten by proteins, for example as a consequence of experience. Despite all the 21st century hullabaloo about epigenetics - changes to the way genes are expressed, without alteration of the DNA sequence - this basic fact remains as true as when Crick, encouraged by Brenner, first described it in an informal document of 1956.

Another feature of Crick’s lecture that was developed in discussion with Brenner was the suggestion that during protein synthesis there must exist a small molecule – they called it the adaptor – that brought each amino acid to the site where they were assembled into a protein. At the same time as Crick gave his lecture, this brilliant prediction was being confirmed, as a US lab identified the adaptor as a special form of RNA.

During this period, one of the issues that obsessed Crick, Brenner and many other leading scientists, including physicists and mathematicians as well as biologists, was the nature of the genetic code. It was generally accepted that DNA, with its four “bases”, was the genetic material in all organisms, and that, as Watson and Crick had put it in the second of their 1953 articles in Nature, “the precise sequence of the bases is the code which carries the genetical information”. But scientists still did not understand the structure of the code, nor how it related to protein synthesis.

Through their endless discussions, Crick and Brenner came to two key conclusions. First, Brenner was able to

Image: The hut building, exterior view, home to the MRC Molecular Biology Research Unit 1957 – 1962. Located in front of the Austin Wing of the Cavendish Laboratory of Physics. Credit: Hans Boye/MRC Laboratory of Molecular Biology.

show by some simple mathematics that the code must be read sequentially, as separate "words" – the letters do not overlap. Then, in a beautiful article (this was the paper with over 800 citations) they actually did some experiments together – even Crick went into the lab – to show that each "word" in the code was composed of three bases (or, just possibly, of some multiple of three).

Moving on from the code, from 1961 the pair charted the future of biology. Once the first word in the genetic code had been cracked, that summer, Crick and Brenner realised that the last of the big questions they had been studying would soon be resolved. The link between DNA and the proteins produced by genes would be fully understood, and they would face a choice – either join the rest of the scientific community in routine research, or find a new fundamental challenge. They chose the latter option, although in one of their final articles together they also decoded the last of the 64 words in the genetic code.

The outcome of those intense, ambitious and high-flying discussions about the future of science was four options. Each of them raised different technical problems and opened different horizons, but all had the same focus: the complete description of a biological system. They considered four candidates, in increasing order of complexity: a virus (lambda), a bacterium (E. coli), the nematode worm (C. elegans) and the laboratory mouse. Brenner's choice – C. elegans – proved to be inspired, combining the right level of simplicity to make the project doable, and sufficient complexity to reveal interesting characteristics that could be applied to other organisms. Crick initially plumped for the bacterium, although he finally veered in completely the other direction and, a few years after leaving Cambridge and Brenner in 1976, turned boldly to neurobiology and the study of human consciousness.

How they discussed

One of the most vivid accounts of Brenner and Crick talking comes from April 1960, and a conversation which led to the experiments that, in summer that year, revealed there is an intermediary between DNA and protein, called messenger RNA (mRNA). This was a key discovery, partly produced by the way that Crick and Brenner interacted.

After a conference in London, Crick, Brenner, Jacob and a number of other researchers returned to Cambridge to chat in Brenner's rooms. They were discussing the latest results from the Paris group of Jacob and Monod, which revolved around a mysterious compound the French had observed in their experiments, which they called "X". At the same time, members of the group were musing about other odd results relating to gene function that had been reported in previous years from various US labs.

"At this point," recalled Crick, "Brenner let out a loud yelp — he had seen the answer". Brenner's yelp was modern biology's equivalent of Archimedes' "Eureka!'.

In his memoirs, Jacob described what happened next: "Francis and Sydney leaped to their feet. Began to gesticulate. To argue at top speed in great agitation. A red-faced Francis. A Sydney with bristling eyebrows. The two talked at once, all but shouting. Each trying to anticipate the other. To explain to the other what had suddenly come to mind. All this at a clip that left my English far behind".

The pair had realised that the two sets of phenomena – X and the weird results from the US – were linked, and could be explained by the existence of a hypothetical transient form of RNA. That evening, at one of the notorious parties held by the Cricks, Brenner and Jacob worked out the detail of an experiment that would help prove their hypothesis, with Crick bringing them beer and sandwiches and making suggestions about their proposed work. That summer, together with Matt Meselson at Caltech in Pasadena, Brenner and Jacob were able to complete their triumphant discovery of mRNA, filling in one of the key gaps in our understanding of how genes work.

This description reveals the intensity of the interactions between Crick and Brenner. It was as though they were not only on the same wavelength, but they seemed to work by telepathy. Gabbling, finishing each other's sentences, speaking in a semi-code that even informed observers could barely comprehend, the two men's minds were effectively one.

But their way of talking with each other was not simply a matter of thinking in the same way, of seeing the same sides of the question. They also both implicitly adopted the same free-style way of bringing in different aspects of the topic, of raising apparently nonsensical possibilities. In an interview with the BBC, Brenner later explained:

"the one rule we had was that you could say anything that came into your head. Now most of these conversations were complete nonsense but every now and again we did this because some half formed idea could be taken up by the other one and really refined."

Mark Bretscher, one of Brenner's PhD students, put it in slightly less decorous terms:"Sydney would pour out all sorts of rubbish, all sorts of crazy ideas. It was almost as though he was on LSD or something. But he wasn't. They were all bits of crazy, making crazy connections... Francis would listen to him and sometimes he would see that there was actually an interesting thought in there somewhere. So Francis acted as the sieve to filter out from the noise, thoughts that would jumble out of Sydney's head."

Swapping ideas is one thing, having your ideas subjected to forensic, and sometimes brutal criticism is another. And yet, for over two decades, that is how Brenner and Crick worked. As Crick explained: "Of course you have to candid. This is perhaps the most important thing. You have to be candid without being rude. So you can say something which sounds rather aggressive but the other

person just knows that's the way you usually disagree with him. So if you say oh that's nonsense, he doesn't turn a hair. And you must of course try and attack the other person's ideas because it's getting rid of the false ideas which is the most important thing in developing the good ones."

There are two approaches to working this way. Either you both have skins as thick as an elephant's hide, or the pair of you are such close friends that nothing said in the heat of the discussion can undermine your relationship. In Crick and Brenner's case, it was most definitely the latter. As Brenner recalled, he found that this interaction with Crick represented "the most important thrill of research, the social interaction, the companionship that comes from two people's minds playing on each other." For Crick, "Collaborating with Sydney not only made all the difference to my ideas and my few experiments, but it was all such fun. It says much for his tolerance and good temper that there was never an angry word between us. Happy days!"

But this frenetic batting to and fro of ideas was not merely intellectual amusement, some kind of superior scientific banter. It had real consequences for the experiments the two men carried out, for their interpretation of their field, and for their vision of the future of biology. Brenner's almost wistful summary of how they worked captures its significance: "I think a lot of the good ideas that we produced were produced in these completely mad sessions."

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Sydney Brenner

The writing on the blackboard

As well as writing to each other and simply talking with – and sometimes at – each other, Crick and Brenner also used a physical support: a blackboard. In the early 1960s, the US biophysicist John Platt visited Cambridge as part of his study of different kinds of scientific thinking and watched how Brenner and Crick interacted. In 1964, Platt wrote up his observations in an article in Science:

"On any given morning at the Laboratory of Molecular Biology in Cambridge, England, the blackboards of Francis Crick or Sidney Brenner will commonly be found covered with logical trees. On the top line will be the hot new result just up from the laboratory or just in by letter or rumour. On the next line there will be two or three alternative explanations, or a little list of 'What he did wrong'. Underneath will be a series of suggested experiments or controls that can reduce the number of possibilities. And so on. The tree grows during the day as one man or another comes in and argues about why one of the experiments wouldn't work, or how it should be changed."

This use of the blackboard was an essential part of Brenner and Crick's approach, which they had transferred to the new Laboratory of Molecular Biology, multiplying the number of boards from one – which they had previously shared in their office in The Hut – to one in every lab. As Brenner recalled: "What we did in the new lab was to equip it with blackboards. We still like simple chalk and blackboards. We had one blackboard in our old little office and we acquired lots of them now. And on these blackboards we would meet, often every day, and talk about anything and everything."

Brenner described in detail how exactly they used the blackboards: "He thought geometrically, like I do, not algebraically. Neither of us would sit down and write axioms and then proceed to deduce answers. We used diagrams a lot. Francis was very good at that too. But we were always careful to keep the scale of things in mind… Francis and I tried very hard to stay imprisoned in the physical context of everything."

At some point in the early 1960s – probably in 1962 – a photographer visited The Hut and took a photo of Crick and Brenner's blackboard. It shows a series of scribbles, written in different colours of chalk, that were linked to experiments to try and decipher the genetic code, with different diagrams relating to different conversations and arguments. You can almost hear their voices as they drew the various simple models or wrote out a primitive sequence of bases, in order to emphasise the point they were making. Prosaically, at the top left-hand corner, is a boxed-off reminder to one or both of them to play a game of squash.

Conclusion

The dynamic collaboration between Crick and Brenner clearly had a tremendous influence on their personal scientific trajectories, and on the way that biology developed from the late 1950s down to the present day. Was the power of their collaboration entirely contingent – flowing from a magic mixture of the people, the place and the time – or are there some principles that can be drawn from the way they worked together that are still applicable?

Contingent factors clearly played a very important role – the two men had the luck of both being brilliant, of striking up a close friendship, and of working at a time when there were great unsolved problems that could be resolved partly by sheer ingenuity. Furthermore, working in an MRC research laboratory at the University of Cambridge, the pair were free of the teaching and administrative responsibilities that many modern scientists have to juggle alongside their research – Brenner confessed to me recently that he never marked an exam in his life.

Discussions with contemporary scientists of what they find frustrating in their work would probably reveal, in negative, what made the Crick and Brenner collaboration so productive. They had the time to throw out ideas, to pursue potential dead-ends without being accused of time-wasting, and above all they were not required to demonstrate in advance the significance of the work they proposed to do. For example, Brenner, Jacob and Meselson just did the mRNA experiment, making use of pre-planned visits to the US, without any extra application for funding or need to justify the impact of the research they planned.

Life has moved on since then, and the number of scientists has increased massively, leading to increased competition for resources, while many experiments involve levels of technical support far greater than those when Crick and Brenner were working together. Collaboration, in particular between specialists in different fields, is increasingly seen as a requirement for producing great science. But the informality of Crick and Brenner's work together highlights something that many of us have lost – time to discuss. If universities and research laboratories were able to carve out some time for their staff to engage in such truly informal interactions – separate from the forced contact of "research away-days" – the results might be surprising, if hard to capture on a spreadsheet.

The real lesson, however, is that early career researchers would be well advised to find a clever friend. Separately, Crick and Brenner would surely both have made decisive contributions to science; together, bound by the intangible ties of friendship, their influence was even greater. Crick and Brenner's collaboration shows that finding someone to bounce ideas off, even in the hurly-burly of modern academic life, can prove invaluable, stimulating new ways of looking at problems, and allowing for unusual and even foolish ideas to be explored and either dismissed or developed. We cannot all reach their intellectual levels, and few modern scientists can enjoy the freedom that their time and place allowed them, but we can all be inspired, and perhaps try out some mad sessions of our own.

Further reading:

The Crick-Brenner correspondence can be viewed online at Cold Spring Harbor Laboratory Archives: https://tinyurl.com/Crick-Brenner

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