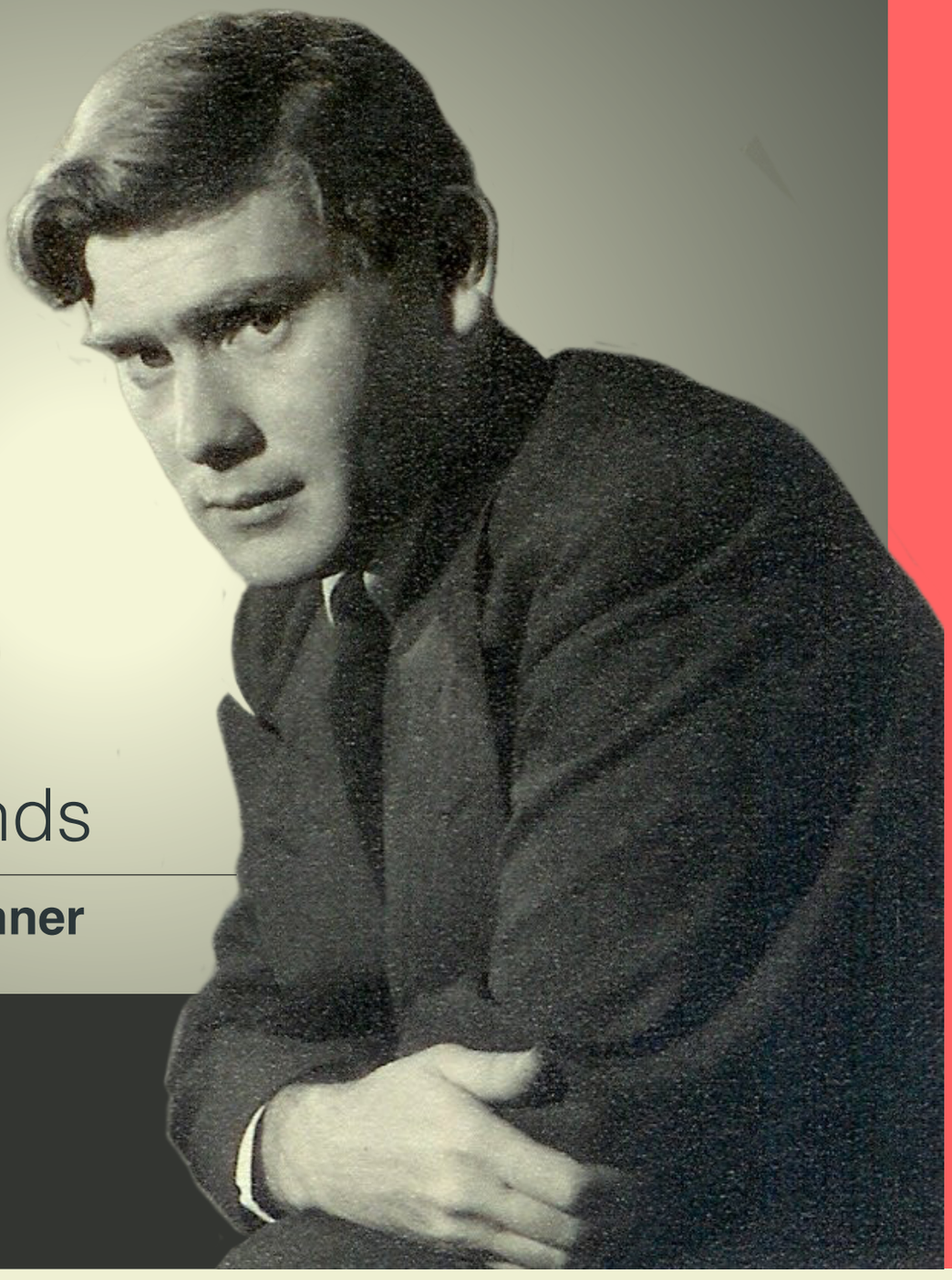
Current Biology



Loose Ends

Sydney Brenner

Editorial

Sydney Brenner's Loose Ends and False Starts

From January 1994 to December 2000 Sydney Brenner – winner of the Nobel Prize for Physiology and Medicine in 2002 and one of the greatest biologists of the 20th century – wrote a column for Current Biology*, initially called Loose Ends (renamed False Starts in 1998, when the column was moved from the back of the journal to the front). The entire set of pieces has now been made conveniently available online via one of the 'collections' highlighted on the homepage of our website. Below, Peter Newmark – the founding editor of* Current Biology *– reminisces about how the column came about and the experience of making sure it came in on time for monthly publication.*

Geoffrey North
Editor

At the time, it seemed outrageous that anyone as busy as Sydney Brenner should be willing to submit to the rigour of writing a personal column to a monthly deadline. Even when Vitek Tracz, the then owner of Current Biology Ltd, first told me that he thought Sydney had agreed to write a column, I imagined this was another bit of wishful thinking squeezed out of an alcoholic lunch and offered up to me as Editor as though it was a *fait accompli* rather than a *grande illusion*. Colleagues of Sydney to whom I mentioned the forthcoming columns chuckled politely, but more at the notion that he would deliver anything on time and with regularity than at the prospect of their content.

We were all wrong. Once Sydney started, he was on a roll. For the first year or so, I continued to be anxious as each deadline approached, there had been no word from Sydney and his part-time secretary – if she could be contacted – had no idea if he was going to deliver a column, let alone from where. On the rare occasion when his secretary could not be raised, I would resort to asking Sydney's wife, May, if she had a contact number for him, but she seldom even knew which country he was in. As Sydney did not use email ("I prefer she-mail", he would pun in unashamedly politically-incorrect reference to his secretary), all I could do was wait by the fax as the deadline approached.

I need not have worried. As Sydney himself put it in the introduction to *Loose Ends*, a collection of his best columns from the first three years published in book form: "[Peter] accepted no excuses about being late for deadlines and I am pleased to say I managed to meet all of these, if only by microseconds in some cases". Whether microseconds, hours or, occasionally, a couple of days before the deadline, the fax would whirr and out would spew a couple of handwritten sheets of prose, as like as not on hotel paper from Singapore or Kyoto. There were very few crossings out, and I wouldn't be surprised if there had been no drafts. Sometimes the fax would be imperfect, but it was almost always possible to fill in the missing or illegible words.

My job was, as Sydney puts it, that of "removing cumbersome phrases and watching for any words that might invoke suits of libel and defamation". On the whole there was little editing to do – Sydney wrote exceptionally well for a scientist and to length, plus or minus a line or two. Now and then the red pen had to be used somewhat liberally, not to remove defamatory phrases (it was much more fun to leave them in) but to add an explanatory phrase, avoid repetition or re-order the text. Only once did I, with some trepidation, reject a column outright: Sydney didn't complain and immediately wrote a replacement.

Without a doubt, the most popular of his columns comprised the letters that 'Uncle Syd' wrote to 'Dear Willie', offering advice to Willie as he climbed the ladder from Graduate Student to Retired Professor (the step before Expired Professor, Sydney would say) – the last letter being penned from Schloss Alzheimer. As this series of columns became famous worldwide, Sydney would half complain that he was now introduced as 'Uncle Syd' when giving a lecture and that he was better known to the younger generation for his columns than for his science. Whereas this would be utterly unjust, I am proud to have been the midwife to Sydney's seven-year stint as a columnist and to what must rank as some of the finest and wittiest popular writing by a scientist in the 20th century.

Peter Newmark
Founding Editor *Current Biology*


Loose ends
by Sydney Brenner
1994

When *Current Biology* invited me to write a monthly column in the journal, I quickly accepted, thinking that I would be able to dash it off easily. I have the freedom to write on anything I choose, subject only to some gentle editorial guidance and also of course to the laws of libel. Writing the column has turned out to be much more difficult than I expected, and the freedom of choice has made matters worse. When I was younger I wrote much more easily than I do now, when I can spend hours, days, even weeks, contemplating first sentences and feeling more and more like a paralysed rabbit as the terrible tiger of publication deadlines approaches.

A good deal of the difficulty comes from the compression of style imposed on us by the editors of scientific journals and the years of writing papers which have to be concise, cautious, impersonal and totally boring. We scientists are discouraged from talking and writing about ideas, and what would be called theory in other areas is dismissed as unbased speculation by the factomania that grips our subject. Some editors allow others to act as commentators on papers published in the journal, and provide them with more freedom of style. Commentators have more opportunity to be clever, witty and to bring some novel insight to the work. Above all, however, they need to be accurate and clear.

Which brings me to the issue of *Science* of the 22nd October 1993, in which there are two very good papers on the identification of genes in *Arabidopsis* and yeast that specify proteins of the 'two-component' signal pathway that had previously been found only in bacteria. This pathway operates by phosphorylation. But the kinase, which is modulated by a receptor, phosphorylates a response regulator on a carboxylic acid group, rather than the tyrosine or serine/threonine phosphorylation that is already very well known in eukaryote cells. The kinase transfers the phosphate from an autophosphorylated histidine and thus (why thus?) is often reversible, with the kinase acting as a phosphatase as well.

The same issue of *Science* has a commentary on this work by Dan Koshland, whose own analysis of this pathway in bacterial chemotaxis is a classic piece of research. Dan is also the Editor-in-Chief of *Science*. I anticipated that I would be served up with fine thoughts that had been kept bottled up for years. Instead, I could not believe what I read. Here are opening sentences:

"Two simplifying principles of biology are what might be called "the principle of redundancy" and "the principle of diversity." Mother Nature follows the principle of redundancy by selecting a simple mechanism or module as a building block for a complex system and then using that module over and over again in other systems. The principle of diversity utilizes the concept that there are many ways of achieving the same goal, for example, creating a living organism or generating motility."

There are certainly some original thoughts here but they are totally wrong. My dictionary defines redundant as "superabundant, superfluous, excessive" and redundancy therefore means that there is more than is actually required. It is indeed a principle, and in engineering it is deliberately used to allow complex systems to preserve their integrity in the face of faulty components. Thus when two, or even three, computers were used in space vehicles this redundancy ensured that everything would continue to work in the event of failure or errors. Redundancy is well known in biology — it is the bane of developmental geneticists. Many genes have been found that, when mutated, show no visible phenotypic effects under laboratory conditions. Such redundancy cannot be deliberate in organisms as there is no Great Engineer in the sky; rather, they must be a consequence of how the system evolved.

Thus, in a simple example, one can imagine a gene product that performs two functions, A and B. If the gene then duplicates and the copy mutates, the product of the copy may perform functions B and C, creating redundancy for the function B. One cannot, therefore, say that the presence of similar schemes in different organisms is a consequence of the principle of redundancy. As for the "principle of diversity", neither is it a principle nor does it use "the concept that there are many ways of achieving the same goal". This is more a question of fact: there may or may not be more than one way of implementing a function or a device.

So what "principles" can these papers illuminate? Koshland uses the term module and he could have lighted on the "principle of modularity" — that is, the construction of complex systems from modules each of which has a closed function and can be assembled independently of other modules. But even this is not exemplified here, and the only principle that is illustrated here is "the principle of genetic continuity". All organisms are connected by descent, and functions evolved by our predecessors are preserved and handed on. Once Nature finds a good device it will have to go on using it because it is impossible to go back to the drawing board and design another one. We owe everything to our prokaryotic ancestors and so it is not surprising that we continue to find prokaryotic systems in eukaryotes; in fact, it would be surprising if we did not.

What still needs to be explained is how the more typical eukaryotic phosphorylation cascades evolved and came to replace the bacterial systems. The principle of continuity demands that there are no unbridgeable chasms to cross in evolution; therefore, the two systems may have existed side by side for some time before one gained ascendancy. That, of course, could be the real exemplar of the "principle of redundancy".

When I retired from the Medical Research Council in 1992, I took the view that retirement should be symmetrical and that, like divorce, it was a question of who was leaving whom. I still have money left over from my Jeantet Prize and this, together with some other private funds, has allowed me to stay on in my laboratory and support a group of scientists. Outside my laboratory there is a plaque that reads "Medical Research Council Unit of Molecular Genetics opened by Dr D. A. Rees on May 11, 1989". When the unit disappeared in May 1991 some wit added a sign that began "and closed by...", but this is no longer there. There was some discussion about what we should call ourselves and, after discussing Sidneyland and BMW (Brenner's Molecular Works), we deleted MRC Unit and remain simply as Molecular Genetics. This is the term invented by Francis Crick and myself in 1958 to describe our work and was the name of our division for many years in the newly founded Laboratory of Molecular Biology. These days, of course, everything is molecular and everybody is a molecular biologist of some kind.

It was molecular genetics, particular of cancer cells, that opened up the field of cellular regulation and identified the components of signal transduction pathways. This has been so productive that those who looked to experimental models such as *Drosophila* and the nematode to provide the basis for understanding complex processes in higher organisms, such as men and mice, have had the tables turned on them. In most cases, when genes that are involved in development in *Drosophila* or the nematode are finally cloned and sequenced it is found that they have already been discovered as oncogenes in mammalian tumours, and that the same tyrosine kinases and ras proteins are at work in both. Except, of course, the outcomes are different, and what is used to make an eye in a fly or a vulva in a worm makes lymphocytes in a mouse.

Like many others, I find it difficult to follow this field in the detail it deserves given that the uncovering of the mechanisms of signal transduction is revealing the molecular basis for cellular processes. My problem is I just cannot remember which three-letter expletive is which; I would not be surprised if at least half of these characters — ras, rac, rib, rob, ref, raf, roc, rol — are not genuine members of the cast. I had the same problem reading *War and Peace,* and had to compile a list of the characters to remind me who they were.

Perhaps somebody will print a handy guide, preferably in luminous ink, so I can take it to seminars. Every one of them that I have attended starts with a slide showing the signal transduction pathway soon to be explained by the speaker. This begins at a receptor at the membrane, pursues its way through the cytoplasm, from second messengers to kinases and kinase kinases and even kinase kinase kinases, with jak and jil, grk and trk, to end in the nucleus with transcription, which is also mediated by a bunch of three-letter factors. There is a puzzling set of activations and inactivations, and everything seems to interact with everything else.

As seminar succeeds seminar, you come to realize that the unique transduction pathway of Dr X crosses, and shares a node with, the equally unique transduction pathway of Dr Y. It dawns on one that this is not a collection of pathways but a network, and that many of the interactions are not required for the explicit transmission of the signal but only to service the network. For example, after stimulation, the network must obviously be restored to its initial state or else it could only be used once and would be useless.

We actually know quite a lot about molecular signalling in other systems and it is useful to look at some cases. For example, an axon conveys messages by modulating the frequency of electrical signals of fixed amplitude. A chemical is then released at the synapse in proportion to this frequency and interacts with its receptor causing some change. If nothing else happened the postsynaptic cell would go into a spasm and would take a long time to relax. Instead, there is either a mechanism for transmitter uptake or an enzyme that destroys the transmitter to ensure that it is delivered as a short pulse with a height that records the frequency of impulses. The G-proteins signal with pulses; not only do they have a built-in decay mechanism but this can be accelerated by GAP proteins, which may be activated by a side branch of the initial pathway to apply this negative feedback.

Another method of signalling is linked to changes in the steady-state level of, in particular, a metabolic intermediate. This method is widely used in bacteria to control the rate of synthesis of metabolites, and allosteric mechanisms ensure that the response is sharply tuned to a narrow range of fluctuations. This requires a reversible interaction of the protein with the ligand, with an association constant corresponding to the critical level. As protein–protein interactions are usually of very high affinity, it is unlikely that this mechanism will be much used in eukaryotes. Steroid receptor proteins probably respond to their effectors in this way, but for molecules such as insulin this is unlikely. Indeed, these act very much like the transmitters; the essentially irreversible interaction of the ligand with its receptor is terminated by the endocytosis of the receptor complex, followed by the proteolytic destruction of both.

If we are to understand how all of this works we will need something more than merely lists of components and binary interactions. As someone once remarked, the great difference between the telephone directory and a Shakespeare play is that, while both have a grand cast of characters, only the play has a plot.

On my visits to universities in America I am often asked to meet the graduate students at what is usually a sandwich lunch session. The faculty carefully exclude themselves, explaining that this allows the students to speak more freely, but my guess is that they want to get rid of the visitor for a few hours and go and have a better lunch elsewhere. We begin by introducing ourselves and our interests. With experience this can be made to take 20 minutes. There follow some penetrating scientific questions such as "What is going to be the next breakthrough in developmental neurobiology?".

Conversation then turns to matters of greater importance — careers, jobs, research opportunities and funding. Finally, we reach a subject much loved by ageing scientists — the good old days. In the good old days we not only did science without any money but, paradoxically, we also came by the money quite easily; a half page was usually enough to get support for a research programme but, if you wanted a building, you might have had to stretch it to a page. Editors of journals were polite, even quite charming in some cases, and they and their referees had not yet become the fanatic guardians of scientific purity that they are today. Elderly scientists were treated with some respect and were not dispatched so easily by grant committees and study sections as they now are.

I have to remind the students that the research community was very small in the good old days and that most of the stresses and strains of the present system come simply from the enormous growth in the number of biomedical research scientists and in their resources and expectations. A large bureaucracy has grown up with administrators, assessors, planners, strategists, palm readers and soothsayers employed to manage the scientific enterprise, so that today we resemble a mediaeval North Indian army with its few thousand soldiers accompanied to war by a few hundred thousand camp followers. Science is a product of human minds, and the essence of research is creative innovation; neither can be produced by committees.

Bemoaning our state and indulging in nostalgia for the past is not a constructive way of dealing with the problem. For some years, instead, I have quietly been conducting research in the fields of science politics and administration. Recently, I have made some remarkable discoveries that not only explain what is going on but also offer some hope for the future. Luckily, this column is not subjected to professional refereeing and I can therefore publish these new theories without being told that I can't use the word new and having them dismissed as idle speculation.

Let us begin with peer review. Peers are ones equals, not superiors. Peers of the realm in England demanded that they be judged by other peers and not by their inferiors, the commoners. Peer review committees originally were enjoined to choose research proposals that met some standard of quality, and those that failed were not funded, even if there was money available. My research shows that the function of peer review committees has changed. Their task now is to ensure that justice has been done to those who will be rejected, because there just isn't enough money to fund everybody who meets the standard. We can now see the subtle working of the theory. The altered function of peer review committees has not affected their structure, or — as better said — the original basis for their structure has been conserved in that their members are requested to be the equals of those being judged. Therefore they must include an ever-increasing proportion of card-carrying mediocrities — those who, were they to apply to the very same committee, would certainly have their proposals rejected. Note, too, that this formulation has correct boundary conditions; as the amount of money declines, so more and more people will be declared mediocre by their mediocre peers and will be entitled to serve on the committees. Readers will recognize that this explains all of their experiences and also why Jim Watson was once moved to say in public that he had looked at one study section and had never heard of any of its members.

This explains the world, but does not help us to see how we can change it. My second study is, I think, valuable in that respect. Health care and its costs are now the subject of careful scrutiny in the United States. My American friends tell me that this could have consequences for biomedical research, and that they are going to be pressurized more and more into applied research. My own, un-peer-reviewed research proves that this is the incorrect expectation and that, if everybody acts consistently and logically, the outcome could be very favourable.

It can be very easily shown that the costs of healthcare are a consequence of two factors: the expectations of those who can afford to spend money on healthcare, and the continuous increase in the technological sophistication of therapy and diagnosis. The ITHT (Immortality Through High Technology) movement is a direct consequence of modern biological research. The more we unravel the mysteries of the immune system, for example, the greater the possibilities for all kinds of interventions, and the more people will have to pay to get them. It therefore follows that biomedical research is inflationary and that its consequences, if successful, are economically detrimental. Research proposals that claim that the results can be applied to a human disease should clearly be penalized, and we should give priority to those proposals that have no potential whatsoever for medical applications. If carefully explained and correctly handled, this presages a renaissance for research in pure or fundamental biology.

I am now busy calculating the financial consequences for healthcare of new knowledge of the genome. Preliminary results are frightening. Clearly, the last genome we should be spending money on is the human genome. I now urge that we look for some beetle in the Amazon forest that is totally useless and divert everybody to work on its genome. We could save our governments billions.

Harold Varmus announced recently that the US National Institutes of Health will now not pursue the patenting of the fragmentary human cDNA sequences that had been generated by Craig Venter. The UK Medical Research Council, which had filed patents on about a thousand cDNA fragments in a defensive action, has followed quickly by withdrawing their application. The French always saw patenting as a threat to the international harmony of the Human Genome Programme and have campaigned vigorously against it. In a magnificent gesture, they had formally presented their cDNA sequences to UNESCO, but unfortunately they had used a commercial cDNA library, and their sequences turned out to be largely from yeast, probably derived from carrier RNA used in the preparation of the library.

I am pleased that public money will no longer be spent on this misplaced activity. I surmise that if we add to this waste the cost of all the meetings, investigations and discussions on patenting the human genome, we have squandered the value of quite a number of research grants and we might have obtained some real sequences for the money spent. It was a mistaken idea to believe that politicians would be impressed by the public medical research organizations' attempt to secure a market value for their work.

Before I explain the patent issues, I need to remind readers of the difference between the scientific and the legal mind. Years ago I attended a meeting on patenting of life forms and met a lawyer in the breakfast queue. "A bacterium is not a plant", he volunteered. I was about to launch into a long discussion of blue-green algae, but thought it best to ask an important question: "How do you know?". Back came the reply, "Because the Supreme Court has ruled so". This is the key; nothing is known and everything is possible until the legal decision is made.

The issues about cDNA fragment patenting chiefly concern their usefulness in industrial application; it seemed ludicrous to apply for a monopoly for work whose only utility was as a means to discover whether they had any utility. We will not know the answer to this question of patentability until it has gone through the entire legal process. If you like, the National Institutes of Health initiated a patenting experiment, and it is a relief to know that no more money will be wasted on pursuing it to conclusion.

Even though the public bodies have removed themselves from the scene, the story is not ended. Venter continues to collect fragments in a private institute supported by a company, Human Genome Sciences, which recently went public. It says it has applied for patents on about ten thousand sequence fragments. Another company, Incyte, has apparently filed patents on an even larger number of sequences. The process of testing whether cDNA fragments can be patented is therefore underway, and I am told that it could take as long as six or seven years to get a final decision if it runs through all the steps of challenge and appeal. Older readers will recall that this is perilously close to the time, the year 2000, when we thought we might have completed the sequence of the entire human genome.

There is one brutal fact that we should not ignore. The sequences already have a market value in that SmithKline Beecham has invested more than 100 million dollars in Human Genome Sciences for the rights to their cDNA fragments. I calculate that, with about 100 000 coding sequences of average length 1 200 bases in the human genome, SmithKline Beecham has potentially acquired all of the valuable expressed information in the human genome for about $1 a base, without having to waste money on any of the introns or other junk sequences. They will probably get very few sequences involved in early embryonic development, but pharmaceutical companies are correctly only interested in targets present in the adults who have the money to buy their products.

What everybody is discovering is that fragments with completely unknown sequences are not very interesting unless you do more work on them. People who purchase sequence fragments are like the buyers of uncut diamonds, who simply receive from the monopoly producers sealed packets of mixed diamonds, some of gem quality and others that are rubbish, suitable only for industrial use. They cannot pick and choose, and must take what they get and then exchange stones with other buyers to repackage them for further use. There are no algorithms nor are there enough computers in the world to tell you that you can make a drug from a sequence fragment; the hard work of extending the partial sequence, expressing it and finding out what it does in the cell cannot be avoided. Each unknown sequence is a research project and even if it is a new member of a known family we still have to find out what it is good for.

Even to an amateur like myself it is clear that the business of the genome is an odd one and different from all the other ventures in the field. It can best be likened to the business of commodity futures; in essence, what people are selling are gene futures, and they ought to be quoted on the Chicago Exchange somewhere between pork bellies and soya bean oil. Over the past year or two, several new genome companies have been formed to generate value from the human genome and are busy seeking alliances with large pharmaceutical companies selling their versions of gene futures.

I invented the cDNA approach about nine years ago and wasted a lot of time trying to convince people that this was the correct approach to the human genome. Eventually we succeeded in getting it started, first in Cambridge and then in London. Patenting the sequences killed the natural development of the project. Here is a classic example of how easily those who administer research can ruin science and turn what could have been a grand achievement into banal rubbish.

A friend recently told me that he had made an important decision as a consequence of hearing a lecture given by Jim Watson at Cold Spring Harbor in March last year. My friend said that the lecture was on "Advice to Young Scientists" but he remembered very little of the lecture except the one statement that had triggered his change in career and which he thought was "if you don't respect your boss and your colleagues, then it's the time to leave". Now, giving advice to young scientists is the surest way ageing scientists can pass into pompous obscurity and because I utterly refused to accept that Jim had reached that point, I was very anxious to find out more about this lecture. It had been delivered at one of those many meetings in 1993 that commemorated the fortieth anniversary of the discovery of the DNA structure. I asked many people who had attended the lecture about it, to try to piece together its contents, and I was just about to try to find out whether it had been recorded when, by chance, I discovered that a written version had been published in *Science* on the 24 September 1993.

That I had missed a paper of such significance proves to me how carelessly I now scan the important journals. However, I have it before me now. The article is called "Succeeding in Science: Some Rules of Thumb" and comes accompanied by an amazingly benign picture of Jim. I will try to summarize briefly what is said in the article. To succeed in science you need luck and you need to be bright, and then you need to apply the following rules. Rule 1 is "avoid dumb people" because it is only the company of bright people that forces out the best in you. Rule 2 is take risks and always be willing to do unconventional things. Since this is liable to land you in trouble, you need rule 3, which is to have something in reserve to rescue you, such as good friends and important patrons. Rule 4 is never do anything that bores you, especially if people tell you it will be good for you. Rule 5 is a kind of notwithstanding rule: it is, stay connected, talk to other scientists (even if they are dumb, see rule 1) and go to meetings because you could pick up some good ideas (even if all the talks are boring, see rule 4). Lastly, there is rule 6: "If you can't stand to be with your real peers, get out of science".

At first, I thought that it was some version of the last rule that had inspired my friend's decision. The cadence is the same, and perhaps what my friend heard and what was written had suffered some divergence. But that doesn't really ring true for it turns on what is meant by real peers; the use of the adjective suggests that these have to be distinguished from the usual, ordinary kind. If that were the case, it is my friend's colleagues, and not him, who should have left, and anyway, the rule deals with science in the large and not with any old job in it. Jim makes no specific references to bosses as a general class, although he has much to say about individuals who tried to play this role in his life. So what we have to do is to apply the rules to bosses; when we do this, it follows that where bosses are dumb or boring or both, that should be enough to put off anybody from staying with them. By the way, any boss who expects respect from the people he works with should immediately be suspect because, in my experience, the best he can hope for is lack of contempt.

I was most relieved to find that Jim had actually not succumbed to the temptation of giving advice, because although he gives us the rules, there is no clue how to apply them in the real world. How can one go about being lucky? And is there any way of being brighter than one really is? I suggest Jim has made the fundamental methodological error, which is common in developmental biology, of confusing a detailed description of a sequence of events with a causal explanation of a pathway. That A succeeds B does not necessarily mean that B causes A; we need additional experiments to prove that connection. Jim's lecture gives a very good account of how things came to be the way they are, but nobody should take the rules as a prescription for how to succeed. To prove causality, we must do experiments, and so we should run history again to find out what we need to change so that Jim would finish up as a second-rate (or even a first-rate) bird watcher. The subheading of the *Science* article is "Reflections" and while this was intended in the sense of contemplations, I have to note these are also what you see when you look at yourself in a mirror.

Peter Medawar wrote a little book in 1979 called *Advice to a Young Scientist* and I dipped into it again recently. The contrast with Watson's lecture is remarkable. Medawar's book gives a picture of science that has totally vanished and now seems remote and archaic, with its emphasis on the methodology and philosophy of science and in dealing with matters such as truth, for example. It is written in a high literary style that many in these punchier times would find strange. Perhaps there is a clue to understanding this difference in my confession that, wherever I use the word bright, Jim uses the word smart. Being smart is more than being bright, just as being bright is more than being intelligent. I always thought that science was about ideas and problems, and that what ought to be prized was solving problems in simple, ingenious ways and finding answers that were not boringly obvious from the start — just hitting on the idea of base pairing, for example. Jim's lecture is not about this kind of cleverness. It is more about being what is called 'street smart'; that is, knowing how to push ahead in the hurly-burly of modern science, where success is prized above anything else.

I almost forgot to divulge my fundamental rule. This is my advice: if you want to succeed in science, become one of the top twenty scientists and, if at all possible, one of the top two.

All the world's a lab ..... at first, the graduate student

Dear Willie

I was so pleased to hear from your mother that you have been accepted as a graduate student by Professor Julius at the University of Calpurnia. Although his group is quite modest — with only fifty people, I believe — you will find an interesting range of topics in molecular and cellular genetics. Of course, you will not be starting research for some time as you have courses to complete; try to get through these as quickly as you can. The essence of scientific research is to get to discover new things and not to spend too much time learning about what has already been done. You will be told that it is good discipline to learn a subject properly and you will have to read fat books called *The Molecular Biology of Something or Other*, but I have found that quite a lot of ignorance is useful in research, because once you think you know everything you won't attempt anything new. Your mentors will teach you how to do experimental research and they will insist that a logical argument is given for every step of the process, from formulating the experiment to interpreting the results. All of this is fine, but don't forget that you can also use your imagination and that a little dreaming is helpful as well.

Many years ago I invented what I call the OSPE experiment. I supposed that there was a mythical scientist working in the Oklahoma School of Poultry Engineering, who lacked all our knowledge and our powers of logical thought, but used his deficiency and ignorance to great effect by performing experiments that nobody else would think sensible and, in so doing, made major discoveries. Therefore, if you want to be a clever scientist you need to be the first to conduct such OSPE experiments, thereby pre-empting our OSPE friend and making sure that he does not receive the acclaim and make fools of the rest of us.

In my time, I have carried out several OSPE experiments, mostly in the dead of night. One of these was to plate out tobacco mosaic virus on *Chlorella* to see whether it would make plaques. The rationale (if it can be called that) is typically OSPEsque; tobacco mosaic virus grows on plants, plants are green, therefore the virus might grow on a green alga, which is, after all, a kind of plant. It did not. Come to think of it, none of my other OSPE experiments worked either. But the beauty is that if it works, you are famous for having a penetrating insight, and if it doesn't, you know that nobody else can be famous either. As it happens, my *Chlorella* OSPE experiment served me well some years later when I had to review a grant based on a weak claim that some growth of tobacco mosaic virus had occasionally been detected in *Chlorella* cultures — the proposer argued with OSPE clarity that the virus needed to grow in chloroplasts.

However, I ramble. Once you have finished your course work you will start on your own project. Alas, you may find it to be a small part of somebody else's research and there may even be several of you working on different aspects of the same problem. Your first experiment is likely to be a mess even if you have followed each step of the protocol designed by your supervisor. Your gels will not run properly and your autoradiographs will be either totally blank or totally black; but don't worry too much, this has happened to everybody and acquiring experimental skills is part of the craft of research.

With practice, you will gain confidence because you will have learned to discriminate between the regularities of an experiment and the vagaries and contamination of the outside world. One of my students once came to me excitedly carrying a Petri dish covered with bright yellow colonies. When I told him to autoclave it immediately, he was most upset and said that I was preventing him from making a discovery like Fleming's discovery of penicillin. I could bet him ten billion dollars that this was contamination and without interest simply because this happens all the time, whereas Fleming's experience is very rare, and I urged him to get back to his research and to try to repeat Watson and Crick's discovery.

You will find that every experiment contains one point that does not accord with the rest. Do not become over impressed by this anomaly. It is usually not a new natural phenomenon. More probably, you either forgot to do something or used a dirty tube, that frequent intruder from the entropic universe. Above all, do not mention it to your supervisor as he might take off into orbit, seeing in it the glimmerings of future fame and making you an unwitting collaborator in this fantasy.

After a while you will find that nobody knows as much about the subject of your research as you do; you will have become the world's expert in it. Your professor will have too much to do to pay attention to such trivia as the work in his laboratory, and he will certainly have no time to keep up with the subject as a whole, only knowing what he hears at meetings or what other people tell him, most of the time over the telephone. You will learn most from the other students, many of whom will become friends for life. Students may be the lowest of the low in a laboratory, but I have to warn you that, sadly, this may be the only time in your career when you can enjoy research as an individual scientist.

Good luck

Uncle Syd

The first well defined proposals on the genetic code appeared soon after the discovery of the double helix. Gamow's 'diamond' code, published in *Nature* in February 1954, proposed that amino acids were directly recognized by diamond-shaped cavities formed on the surface of DNA by components of three successive base pairs. As a cosmologist, he was not too bothered by the physical details of his model, and he proposed that the diamonds could be read in equivalent ways. Direction did not matter, nor did base pair orientation, which collapses the 64 triplets into 20 classes, 8 with two, and 12 with four, representations. The fact that the magic number 20 corresponded to the number of amino acids in proteins impressed theoreticians, who were willing to overlook the implausible physical postulates of the model. The comma-less code of Crick, Griffith and Orgel also produced the magic number 20 in a simple and elegant way, as did Gamow's alternative combination code, but the last was physically implausible. Francis Crick put all of this theorizing to rest by his adaptor hypothesis, which proposed that each amino acid would be coupled to one or more adaptor RNAs by a specific enzyme. Thus, the degeneracy of the assignments of codons to amino acids could be anything and the code would have to be found empirically. That was the way it happened and we now know that, in addition to the 20 amino acids, there are triplets for chain termination and some codons are used both for chain initiation and for coding. The magic number is therefore 21, and possibly 22.

When the code was finally defined, people began to speculate on why it took the form it did. Some believed that the structure still reflected the direct stereochemical recognition of amino acids by nucleotide codons. In 1968, Francis Crick produced the 'frozen accident' theory, which argued that the code evolved more or less by chance and then became fixed in its present form because further changes would produce too many damaging alterations in proteins. During the 1980s, a whole series of discoveries revealed that there were departures from the genetic code, not only in mitochondrial genomes, where they were first found, but also in nuclear genomes, whereupon Jukes and his collaborators proposed a 'codon-capture' model to account for these deviations. This, of course, raises the question of the extent to which the present code is itself the product of previous codon-capture events; indeed, some of the present amino acids may have entered the code in this way.

It is still interesting to ask whether the present code preserves some feature that, if properly extracted, could illuminate its origin and evolution. The further back in time we want to go, the more hopeless this task seems. For example, there may have been a more primitive set of amino acids, such as ornithine and homocysteine, which preceded modern arginine and methionine. The present repertoire of activating enzymes can tell us very little because they could have replaced earlier versions.

For these reasons, I cursorily dismissed the account given by John Maddox in *Nature* early this year of the work of Hornos and Hornos, who claimed to have explained the present structure of the genetic code by a unique sequence of symmetry-breaking steps. Later, I was sent a copy of a note on the same work by Ian Stewart in the 5 March *New Scientist*, and as I could not really understand what had been accomplished, I decided a few weeks ago to read the original paper.

The paper, entitled 'Algebraic Model for the Evolution of the Genetic Code', by J.E.M. Hornos and Y.M.M. Hornos can be found in *Physical Review Letters* 1993, **71**:4401–4404. The authors do indeed state that their main goal is to search for symmetries in the genetic code and this "leads us to Lie group theory and the Cartan classification theorem". I do not pretend to be even a novice in these fields, but, as I understand it, the authors begin with the distinctive pattern of the genetic code, which has different assignments of amino acids to 1, 2, 3, 4 and 6 codons. They show that they can generate this pattern by a sequence of symmetry-breaking operations beginning with a primordial code which has six elements (five amino acids and termination) with degeneracies of 2, 4, 10, 16 and 20. The next step generates 14 elements, then 16, and finally 21 with the present pattern. Actually, it should produce 27 so they need to postulate a quenching step.

Codon capture immediately tells us that we should distrust this result, but we can go on and ask for the physical meaning of the symmetry-breaking process. I would have thought that it would refer to some property of the codons so that a typical symmetry-breaking operation would be to go from GAN for a primitive acidic amino acid to the present GAY for aspartic acid and GAR for glutamic acid. They associate the classification with the polarities of amino acids through some complicated calculation, and use this to assign the triplets to amino acids. This must be wrong. It has to be the other way around because evolution of the code proceeds hand in hand with the evolution of messages and their proteins. Because each step of elaboration must satisfy the constraints of protein function, any "symmetry-breaking operations" will themselves result in the well known feature of the code that related amino acids have related codons. It cannot be the outcome of some algebra, as the authors would have us believe.

The trouble with theoretical physicists is that they produce theories so deep as to have lost touch with reality. I hope this one is so deep that it sinks without trace.

All the world's a lab ... then the post-doc

Dear Willie,

I met Gus Julius at the Hot Air Arbor Symposium and was delighted to hear how well you have done in his laboratory. He told me that you had succeeded in cloning the gene for plethorin and that you can now explain many functions of the cell by the versatile properties of this widely distributed molecule. I understand that you are now busy writing your thesis and some papers and I assume that you will shortly start applying for post-doctoral fellowships and deciding what to do and where to go.

When I was young all of these were simple decisions because there were hardly any fellowships available and most of the subjects that we were interested in had not been invented. Even their names did not exist and all you could hope for was that the place you chose would provide you with at least an entry to that mysterious amalgam of genetics, cell physiology and physical chemistry that was not mere biochemistry. And if you grew up in South Africa or Australia or even Canada you went to England, the country you had heard about in history and geography classes and whose poets and writers you had studied in English lessons. Those of us who had any go went to the centre to try ourselves out and we thought it better to be a small frog in a large pond than an enormous tadpole in a small one. And this still holds: go to the centre or get as close to it as you can.

The most perplexing question is to decide what research you are going to do. Should you stay in the field of your graduate research or move to a different area? Should you do a safe but perhaps pedestrian project or should you take a chance and try to do something that is new and exciting? It is hard to give very specific advice, especially in these uncertain days when only the old and established can afford to be radical and reckless, whereas the young have to be conservative and careful. You should first try to discover within yourself what it is that interests you passionately and what problems you would like to solve; then you only have to satisfy yourself that your next step is on that path. Anyway, today nearly everything in biology has become closely connected: going from cell biology to neurobiology may only mean a change of names, such as calling cells neurons, or adding a little bit of two-dimensional biochemistry and some electricity.

When it comes to important questions, such as whether to go to a small or a large lab, I can offer you serious advice. A post-doc is only a stepping stone to the next stage and you must make sure that in the course of a few years you will move to the next stage, and not just to another post-doc, because the latter, even if it offers a wonderful life style with surfing or back-packing or both, is actually the beginning of the end. To move onwards and upwards you have to get your own story and this should have some distinctive visibility. Therefore the laboratory you choose should have enough to give away so that you can take a piece of it with you when you leave to set up your own laboratory. If the laboratory is small, there may well be good reasons for it. Probably it has only a small pie to cut up. In a large lab, the pie has to be cut up into many more pieces, but it could be a much larger pie.

All of this requires fine judgement but it is only the zero-order approximation to the complete solution. As the head of your prospective laboratory was himself at one time a post-doc, you should go back recursively to the laboratory where he started his career and make a special study of it because that is where he got his scientific patrimony. Furthermore, such is the rapidity with which academic generations succeed themselves that you may have to repeat this study several steps back into the lineage.

You may not know it, but it was the system of all the sons inheriting equally that ruined the French aristocracy and brought them to their knees, often under a guillotine. I once explained this to the Director of the Pasteur Institute in a discussion on the allocation of resources, and I also emphasized that cleverly arranged marriages could not hope to compensate for the exponential dilution. The English preferred to practise primogeniture, where the eldest son got everything and the rest had to go away and become clergymen, colonial governors, soldiers and, in more recent times, businessmen and university professors.

Thus in analysing your laboratory you will need to note how much the scientific capital has been diluted by inheritance or enhanced by lucky marriages, and also how many of the post-docs have been second sons and gone to biotech companies, taking nothing with them.

I am sure you will make the right decision when the time comes and I hope to hear from you soon. In the meantime get your papers and thesis written. Remember that the next professor you are going to make famous has got to be yourself.

Off you go to work.

Uncle Syd

At least one of my readers has complained that I write about too narrow a range of science and that I need to widen it. I cannot bring you news from the worlds of astrophysics and quantum mechanics but, as always, I try to please my readers, so this month's column is about the brain. In the 1960s and 1970s, some molecular biologists began to entertain notions that they could succeed equally well in other fields of biology, and that the neurosciences could benefit from their attention. Several of my friends professionally transformed themselves into neurobiologists and have even written books showing how modern biology proposes to deal with abstruse and age-old questions such as consciousness, mind/brain dualism and even the soul.

Actually, I have quite good credentials for entering this area because many years ago I worked on the anatomy and physiology of the primate brain. My vintage is that of beeswax and the smoked drum, going back nearly 50 years now, but you will see that I know what I am talking about.

Quite a lot of modern research on the brain is focused on vision, largely because our knowledge of how the brain analyses visual input is extensive, but also because many people work on it. It is also an area much favoured by machine-minders. Of course, I do not disparage any of this work, but it seems to me that there is another area that has been neglected and which I think has great potential. This is the theory of itching, which is not a branch of Chinese metaphysics but your plain, common or garden itching and its concomitant scratching, which also has nothing to do with Taoism. I know that I scratch an itchy patch because it gives me relief from that demandingly irritating sensation. I know I do it consciously because an itch, like pain, grabs you, and viciously itchy mosquito bites can even wake you from a deep sleep. I am also certain that all of this subjective knowledge is shared by thousands of co-sufferers from psoriasis, insect bites and other itchigenic agents.

Naturally, what we want now is a scientific account of these phenomena so that we can reach a new and deeper level of understanding the itch. In the short space available I can only sketch an outline of a research programme for this field; unfortunately, it is unlikely that research will be funded because, unlike cancer and heart disease, itching is not life-threatening.

Fundamentally, we will want a neuronal account of what goes on in the brain starting from the itch and finishing with the scratch. Are there special itch receptors in the skin? What is it in an insect bite that stimulates them, or do we have intrinsic elicitors which are released by the skin in response to many sources of irritation? Where do the nerve fibres carrying the sensation go? After the sensory cortex, are there connections to other parts of the brain, such as the frontal cortex?

Then we have to analyse the scratching pathway, and ask about the levels at which the two are connected. Are there connections in the spinal cord, so that there is a scratching reflex? The motor cortex will presumably be involved in generating the scratching and the question is whether it receives inputs from parts of the brain where we might locate intentionality and even, perhaps, consciousness. All of this could be studied by a variety of techniques: ablation experiments could resolve whether there is a scratch reflex, but it would be very nice to study activity directly in the brains of alert subjects to see which areas are involved in being conscious about itching. We could extend the analysis from itchy subjects to itching subjects describing their sensation of itchiness.

We can readily observe that animals other than primates also exhibit a behaviour suggesting that the itch–scratch pathway is operating. Perhaps this is just a reflex, but from watching dogs I am convinced that they are conscious of the sensation of itchiness. This could be proved by analysing the brain centres involved. For example, we might find that other primates have activities corresponding to everything except those concerned with talking or writing about itchiness; for other animals we could check whether they are conscious of the itch. Perhaps we will discover that fish can itch even though they can't scratch. The question of whether computers can be itchy would be excluded as obviously ludicrous but we could clearly use them to solve the complicated equations of the dynamics of the pathway.

When my colleagues and I began our work on the simple nervous system of the nematode we asked two questions. Could we determine the wiring diagram of this system? And, if so, could we compute behaviour from it? After many years' work we answered the first question and we were able to work out all the connections of all the neurons and to learn a little about their transmitters and the activity of these at synapses. The second question has not yet been answered. It is at once too simple and too difficult. Too simple, because nematode behaviour is seen as too elementary and uninteresting; people want Behaviour with a capital B. And too difficult, because it needs a lot of detailed knowledge to solve it correctly, and then even if a solution could be found we would face the tricky question of proving that it is unique and that no other equivalent solutions exist.

Neurobiology still has a long way to go to contend with consciousness. Perhaps we should be content to work instead on unconsciousness for a while, and find out about all those processes going on in our brains that we don't know about directly and need science to tell us the answers.

All the world's a lab ... then the assistant professor

Dear Willie,

How time flies! It seems like only yesterday that you were starting your scientific career and now I have news of your appointment as Assistant Professor in the Department of Pathobiology at the University of Santa Francesca. You were wise to go into the field of cell death during your postdoc, even if it did mean changing labs. Once it was the life sciences that were the centre of interest but now every university will be founding Institutes of the Death Sciences. It seems to me that half of the pharmaceutical world is trying to stop cells dying while the other half is trying to find drugs to kill cells. I have even heard rumours of a new journal, Molecular Thanatology.

You did not tell me how much teaching you have to do. As the newest recruit to the department, it is likely to be quite a lot and, naturally, everybody who is going to off-load their work onto you will tell you that teaching will do you good. When I was a student, I was taught bacteriology by somebody who simply read back to us the lecture notes he had taken as a student some 25 years earlier. As the material had a distinctive late Victorian air about it, I surmised that it had passed through more than one generation of transmission. You need not go that far but you should not waste too much time in designing your lectures because, whereas teaching small groups of advanced students can be very rewarding, addressing hordes of rowdy undergraduates is a thankless task. I know because I have served my time in the galleys, teaching biochemistry to dental students. What on earth the Krebs cycle had to do with drilling teeth was beyond me as well as my unfortunate students.

Your main task will be to establish your research, and for this you will soon have to write your first grant application. This is a special art which you will need to master, and here are a few tips. Firstly, you will never again in your life write about any subject in as much detail. Leave nothing out, especially in describing how you are going to do your experiments. Secondly, you will need to convince the committee that everything is going to work — so don't raise any questions, even if they are the kind of questions that we should be trying to answer in research. Thirdly, don't be too original, as your ideas may somehow penetrate the unconscious of your reviewer and emerge later as his novel research. Finally, make sure you have quoted absolutely everybody because there is nothing that annoys reviewers more than to find no mention of their epoch-making work.

These are parts of the standard recipe, but they do not go to the heart of the matter. Experienced scientists will tell you that you should only apply for grants to support work that you have already done but not published; this gives you the freedom to use the grant to do something else which can then form the basis for the next application. However, to carry out this simple strategy requires that you have some scientific capital in hand, and for people like yourself, just beginning, the trouble is that you have not had any time to accumulate any capital.

I have for long entertained an elegant solution to this difficulty, and that is to found a bank, BISCUIT (Bank of International Scientific Capital and Unpublished Information and Techniques), that will lend scientific capital to first-time grant applicants and others in need. It will not only lend ideas for research but also loan experiments that have been carried out but have not been published. We have to be careful with the latter, because although such holdings are of high value they could undergo instant depreciation if someone else does the experiment and publishes the result. Where, you ask, does the bank get its capital? No problem. I know a number of scientists who have a surplus of scientific ideas and lots of experiments that they find too boring to write up and these 'wealthy' individuals would be the first investors. The bank would also continue to receive deposits. Once we got going, everything would be fine, because the borrowers would not only have to pay back capital but we would charge interest so that our holdings grew. And, of course, if any depositor were to suffer a catastrophic career collapse, he could withdraw all of his capital and start again. The beauty of it is that he would get new, up-to-date ideas and experiments and, in this way, his original deposit, although used a long time ago, will have retained its value and will not have been corroded by time. I am amazed that in these times of high-powered service industries nobody has thought of doing this before, but perhaps that's because it is only scientists who will profit from the BISCUIT bank.

I have had many postdoctoral fellows who swore that they would continue to stay at the bench themselves and never build up large groups. Alas, within a few years, their groups had grown and they were fully engaged in writing grant applications, renewals, extensions and reports to sustain the research they now could not find the time to do and for which they needed a large group of students and postdocs to fulfil the promises made in the grants. I have no real answer to this perplexing problem. Perhaps one should aim at being only moderately successful, but I feel that is too metastable a state, poised as it is between the disappointments of failure and the regrets of total success.

Don't pause to think too much about it; write your grant proposal.

Uncle Syd

I recently went to yet another meeting on the Human Genome to discuss how it was going to help us advance our understanding of human disease. One now hears less of "We will be able to ....." assertions and many more "How can we.....?" questions. How can we decide that this region is relevant before we commit large resources to sequencing megabases of DNA? How can we find the functions of unknown genes?

The last question brings us to transgenic mice and how models of human diseases can be made by disrupting genes and producing the so called knock-out mice. Although it is still quite difficult and expensive to create and maintain such KO mice, it has become much easier to do since the thought dawned on people that the best way to achieve homologous recombination efficiently is to use sequences that are homologous and come from the same mouse strain from which the ES cells in which the recombination takes place were derived. There is now a growing collection of KOs and many have already proved enormously valuable in many branches of biological research and especially in immunology.

There is, however, quite a frequent feature of such experiments that is alarming the people doing them. It appears that a large fraction of KOs either have no discernible phenotypic effect, or one that is surprisingly less severe than one might have expected. This has raised the ugly question of redundancy — that is, the possibility that organisms have more genes than they really need, and have multiple ways of achieving the same end. The same has been found in yeast where many KOs of newly discovered genes produce apparently normal phenotypes.

We have to be very careful about how we look at redundancy in higher organisms. It could be argued that increasing complexity brings with it increasing unreliability, and to compensate for this multiple pathways have been created in evolution. But this is a designer's language and not that of natural selection; while natural selection may work in a different way to enhance reliability, it certainly cannot do this to protect against genetic mistakes. In fact, that has already been achieved in evolution by making most complex animals and plants diploid, giving them two copies of every gene.

All of these KO experiments are carried out with laboratory strains of organisms; inbred strains of mice are used, yeast cultures are clonal lines, and we work with isogenic flies and isogenic worms. Classical genetics demanded this uniformity of genetic background for experimentation because anything else was a mess. Many people are certain that if apparently normal KO mice were let out into the real world they would have little chance of survival, but that is probably also true of their pampered 'wild-type' progenitors in the laboratory. Life out there is tougher than life in here, but that's ecology and not genetics.

The interesting answer comes from experiments in which KO mice have been outcrossed to other laboratory strains and the gene disruptions studied in other backgrounds. Quite often there are remarkable modifications of the phenotypic expression of the mutants, and a mutant totally innocent in one background exposes its guilt in another. The process of crossing often exposes several genetic differences between the two strains, as shown by the segregation of variable phenotypes.

Classical experimental geneticists — and there are fewer and fewer around each day — know all about this. 'Leaky' mutants abounded in phage and bacterial genetics, and *Drosophila* genetics was full of modifiers, enhancers and suppressors, with mutants that were often described as having 'poor penetrance or low expressivity'. I once thought I knew the difference between these, but it didn't matter because everything that had any phenotypic variability was avoided. We taught our students to throw these mutants away because there was nothing serious that could be done with them. Genetic analysis was hard work: one had little hope of identifying the gene product of the modifier and, with the exception of the nonsense suppressor there was no way to understand how these might function in the organism.

I found many such mutants in *Caenorhabditis elegans* with variable phenotypes. This was not caused by background variation nor always the result of leakiness, as there were genes where every allele had the same variable phenotype. I speculated that perhaps biological processes in complex organisms had two functional components: a kernel process that produced a very inaccurate result and a refining processes that improved accuracy. The latter could be seen as optimizing the phenotype and could quite easily be selected by natural selection. For example, it is not possible to count single molecules accurately in biological system, and one can easily imagine how the concentration of one gene product could be regulated by selecting for mutants in other genes that controlled this by feedback inhibition, for example.

Today we have the means to analyze these contributions to the phenotype. KO mice with a phenotype whose expression is subject to other genes and to environmental factors should not be objects of despair but beautiful models that will throw light on the complexity of organismic function. And, incidentally, if we worked on such KOs we would gain a much better picture of the messy but real world of human disease susceptibility. The genome is certainly not a collection of 100 000 commandments with everything carried out by dead reckoning.

All the world's a lab ... then the associate professor

Dear Willie,

Things are really going well for you. I look forward so much to reading your papers and to seeing how your research is developing, even though all the theory is beyond me. I never did learn mathematics properly and so I find it quite hard to follow such matters as canonical four-dimensional manifolds. In my field, all you had to know was how to count to 20 and a little about the Poisson distribution so that you could calculate the multiplicity of infection of your bacteriophages. Long ago I tried to prepare myself for the 'new biology' by investing some time in learning mathematics that might be needed in the future. As nobody was quite sure whether this was going to be group theory or lattice algebra or statistical geometry I sampled all of them until I realized that first you have to be clear about the nature of the problem, and then you can profitably go and look for the tools to solve it.

I am amazed that you can continue to get support for your research on such a lavish scale. Everybody knows you have solved an important question in learning, but I suspect that many of the reviewers of your grants are, like me, unable to comprehend what you are doing and simply approve your applications because they would be too embarrassed to admit their lack of understanding. Of course, it could quite easily have gone the other way.

I almost forgot to congratulate you on your promotion, but a few words of advice. Now that you have attained the exalted status of a tenured professor and as you approach the midpoint of your scientific life you will be pressed to accept doing things outside your primary role as a researcher and teacher. You will be asked to serve on committees both in your university and outside, and often it will be put to you that this is a duty you should perform. Such requests are inescapable and the only way I found of dealing with them was to decide that I would serve on only one committee for each organization to which I felt I owed something; if they asked me to join a second one, I told them of my rule and that they would have to get me off the first one before I would accept the new one. As all committees are useless it didn't matter to me where I paid off my real (or imagined) debts.

This worked well for a while until I discovered that the numbers of organizations had multiplied and that I would need a more effective method to contain the demands. I learnt very quickly that the only reason that would be accepted for not attending a committee meeting was that one already had a previous commitment to attend a meeting of another organization on the same day. I therefore invented a society, the Orion Society, a highly secret and very exclusive society that spawned a multitude of committees, sub-committees, working parties, evaluation groups and so on that, regrettably, had a prior claim on my attention. Soon people wanted to know more about this club and some even decided that they would like to join it. However, it was always made clear to them that applications were never entertained and that if they were deemed to qualify for membership they would be discreetly approached at the appropriate time. A friend of mine was so impressed by the concept of the Orion Society that he brought it into being as a non-society and for a short time its only function was for a small number of non-members to meet at dinner to celebrate its non-existence.

I have left you in my will a small black book with details of this and other schemes for dealing with intrusions on one's time, but there are a few more pieces of advice that you will need more immediately. A crucial one is how to treat invitations to attend scientific meetings, or to give lectures. I have found that only the young and the old enjoy receiving such invitations; the young, because they wait to be remembered, the old, because they do not want to be forgotten. You need to have a good excuse to be able to decline, but it must be general and capable of wide application. The solution is the perfect tautology. Thus, when you are invited to attend a meeting, you simply reply "Dear Dr X, I regret that I am unable to accept your invitation as I find I cannot attend your meeting. Yours very sincerely, etc". Many variations of this theme can be produced and some of great subtlety exist. The best can even evoke such replies such as: "Thank you for your courteous letter. We quite understand, and although your contribution will be missed etc".

I hope you don't think that I should have spent more time on my research and less on these schemes. They are inventions in their own right and they kept my mind occupied and amused. They also sometimes distracted me productively from the boredom that accompanies so much of research.

With fond regards

Uncle Syd


Loose ends
by Sydney Brenner
1995

I had hoped that at least some of the more controversial pieces I have written in the past year would arouse enough indignation to allow me to write an anniversary column replying to some of the more outraged and pompous correspondents. Sadly, I have had only one letter that fits the bill, containing words such as "I was considerably offended by Sydney Brenner's article". I hasten to add that I have received other letters as well, but unfortunately these have been only complimentary and informative.

My offended correspondent was upset by my remarks on peer review and complained about my theory that peer review committees must regress to mediocrity. He felt that this did not apply to NIH study sections, which he thought was suggested by my piece, although I was careful not to mention any names. I was extremely pleased to read a few weeks ago that peer review is about to be reformed in NIH; one of the significant changes will be to add individuals who are knowledgeable to the committees. Although I cannot claim to be responsible for these changes (much as I would like to), it does seem that regression to mediocrity is now being taken seriously. One of my more cynical friends has pointed out that the only way to be completely fair in making decisions on grant applications is to have a committee that is totally ignorant and uninterested, thus ensuring that any prejudice or bias that could arise from knowledge of the subject is completely excluded. We should, however, accept that research is an elitist activity, requiring superior abilities of thinking and doing, even though there are now large areas of biology in which research can be carried out almost by prescription if one knows where to buy the kits and has enough money to pay for them.

Having succeeded so rapidly with peer review, I intend to make 1995 the year to reform scientific publication. It could do with reform because everybody seems to have a grievance. Authors are infuriated by the cavalier way editors and referees treat their great works; editors complain about the huge number of boring and repetitive papers they receive; and referees whine about the rubbish they have to waste their valuable time on reading. When one realizes that quite often these are the same people, then it is obvious that we have a serious problem.

Everybody in biology knows that there is a growing divide between what is considered as important news and what is a worthy, but not greatly novel or significant, addition to the archive. Some journals believe it is their right and duty to bring only breakthrough news to their audiences, leaving the great body of research to go the 'more technical journals'. Because of this avowed policy, the journals have high visibility, reinforced by the desire of everybody to appear in their pages. While many agree with the policy, not all — and especially those who are not chosen — would agree with the criteria of selection. It carries the danger that all select clubs engender, namely that those blackballed from the club will go off and form their own club from which, of course, they can exclude others. This can easily be repeated, and so journals will continue to multiply as long as there is a group who feel excluded. Getting one's work published and getting it into the right journals has become almost as difficult as doing the research itself.

The main problem we face is what to do with the endlessly growing archive of scientific results embodied in shelf after shelf of massive bound volumes of journals. To read an article becomes a test of physical strength and I hope that libraries carry enough insurance to cover injuries to elderly scientists working in the stacks.

The answer, everybody says, is electronic publishing. A few days ago I answered a questionnaire from a scientific society pondering the future of its scientific journals. Respondents were given a choice of five statements about electronic publishing, ranging from the wildly radical — electronic publishing is here, burn all the journals — to the deeply reactionary — electronic publishing will never succeed, throw all computers away. What was remarkable is that I found myself in partial agreement with every single one of the propositions offered. Yes, electronic publishing is the right answer; yes, widespread use of it is still in the future; yes, some form of printed journal will still be required. The printed page is still very important to me, and not only because I can read it in places where it is difficult and inconvenient to handle a computer. I love to browse in libraries and to see the new journals when they come in, and I fear that making the archive electronic will mean that a large amount of science will be directly consigned to electronic oblivion without passing through anybody's brain at all.

The biological sciences have to be concerned with detail because living organisms are products of evolved genomes and cannot be encapsulated as solutions of differential equations. It will be important to find all transcription factors and all of the sequences they bind to and we must avoid treating the first instance as breakthrough news and the subsequent cases as repetitive. And putting everything onto disc does not guarantee that it will enter anybody's conciousness. I once pointed out that if you want to keep something secret in molecular biology, publish it, preferably in a technical journal.

What ever happens, we will need an intermediate group of people to draw our attention to what is going into the archive and where it can be found. In fact we have them now — writing reviews. Their role will become more important and rather like that of the critics and reviewers in the literary journals. So when you are asked "Have you read this article in the journal?" you will then be able to reply "No, but I've read the review".

All the world's a lab ... then the full professor

Dear Willie

Wonderful news! Congratulations on your new professorship, election to the National Academy and the Ciba-Merck-Glaxo-Roche-Smith-Sandoz-Johnson Prize for Neuropharmacology — and all in the same week. I know several cases where the award of a Nobel Prize produced a frantic scramble to elect the person to their national scientific society, which had up to then not regarded them as suitable candidates for membership. At least that won't happen in your case should you make the winter trip to Sweden at some future stage.

I rather like the fact that you have the title of Distinguished Professor as it suggests that you can be promoted to the next level of Extinguished Professor, much in the same way as one wants to elevate some Visiting Lecturers to Non-Visiting Lecturers. I have to be frank with you and tell you that I do not care for your suggestion that your full title is Distinguished Professorship of Genetic and Developmental Psychoneurobiology. This is too long, too cumbersome and too boring. You need to use the opportunity to invent a new name or subject. I suggest Molecular Philosophy, or Cytology of Mind as being more suitable. When I had to choose a title, I alighted on Genetic Medicine, partly to distinguish what I was doing from Medical Genetics, but largely in the hope that some printer's happy error would convert it into Generic Medicine, much as Theoretical Physics has been transformed into Theatrical Physics and Neural Ethology into Neural Theology.

You will find that one sad consequence of rising in the outside world will be the growing divide between yourself and your scientific research. Not only will you find less and less time to spend in the laboratory but the work itself will lose its individual stamp as it comes to be carried out by more and more people both within your own group and by others outside your laboratory. In fact, all outstanding research could be said to be doomed to this success, so have no fear, the work will get done by all those whom you have attracted into your field, and, in a sense, you will have become dispensable. The man who said that it was not the arrival but the journey itself that counts did not know much about scientific research. Everybody waits to arrive but unfortunately arrivals are few and far between; most of us are engaged in the hard work of the journey itself, which can be meandering and pedestrian. There is, however, a ray of hope in the thought that all journeys have to start as well as end, and that departures are not only more creative than arrivals but can be just as thrilling. You should always keep in mind that you can start again.

While you are pondering these deep questions, you should ensure that you lessen in every possible way the impact of the outside world. You will certainly now be invited to serve on committees where matters of national science policy will be discussed and purportedly important decisions are made. You may not be able to avoid these invitations and you may even think that a person such as yourself, a working scientist, is exactly what these committees need to produce sensible results. Actually, what you will find is that these committees are run by administrators who have already decided what answers they want and hope that the committees can be directed by the Chairman to give these answers. I found a good way of dealing with this, and will pass on the secret.

One of the problems of committees is the vast amount of paper that is sent to you before the meeting. For one organization in London, I observed that only those committee members who came from Oxford and Cambridge had ever the slightest idea of what was in these papers, because they read them on the train going up to the meeting. London-based colleagues knew absolutely nothing and had to improvise. The Chairman was briefed before the meeting and his crib gave him instant superiority. What you need to do is to find some minor obscure point buried deep in one of the appendices and to raise it, just before the Chairman passes on to the next item, in a quiet but penetrating manner, heavily embroidered with a lot of difficult technical stuff, which the administrators do not understand. All of your colleagues will instantly support you and, not wanting to show ignorance or negligence, will produce more complex technical arguments that will compound the confusion.

You only have to make sure that the point is neither so damning that an excellent proposal is instantly dismissed nor so praiseworthy that a mediocre proposal is passed with acclamation; the true art consists in getting it sent back to the administrators for further analysis and recasting. This not only delays that particular decision, but will hold up everything else as well while the administrators grapple with your arguments. When finally they produce something that deals with the point you raised, you blandly admit that you were wrong at the time, and want to go back to the original. You can do this because the hallmark of a scientist is to be able to change one's views depending on evidence; no administrator can do this.

I shall watch your progress with interest. As ever

Uncle Syd

I have received several invitations to genome meetings and been asked to talk on subjects such as "After the Human Genome — what next?" or "From sequence to function — prospects for the future". As was predicted at the beginning of the Human Genome Project, getting the sequence will be the easy part as only technical issues are involved. The hard part will be finding out what it means, because this poses intellectual problems of how to understand the participation of the genes in the functions of living cells. The Human Genome Project was once compared to putting men on the moon and the similarity is deeper than just the cost: sending men to the moon is easy, it's getting them back that is costly and difficult. The real work in biology is now only beginning and we are now entering what Jurgen Drews has called the post-genomics phase.

How does one go from sequence to function? In classical experimental genetics, genes were identified by finding mutants. There was no other way to define a wild-type gene; we needed the mutant allele with a phenotypic alteration. Mendel could not assert that there was a factor (gene) for the character of tallness until he found dwarf mutants displaying a lack of tallness. Although we had great difficulties in resolving the functions of any particular gene at the molecular level, the mutants were selected for altered functions and thus experimental genetics was rooted in physiology. By itself, genetic analysis — the isolation and complementation of mutants — gave us only a classification and told us something of the grammar of the system. With very few exceptions, it was not possible to come to any deep conclusions about function and structure. Only when genetic analysis was coupled with powerful methods of *in vitro* biochemical analysis did the full power of this approach emerge.

In fungi and bacteria, for example, nutritional mutants (auxotrophs) opened the door to the enzymology of small molecule biosynthesis. A mutant extract provides an assay system for the purified missing component, and this was also the method used in studying DNA replication, where many new components were discovered by using conditional lethal mutants of DNA synthesis. Bacteriophage self-assembly is another example where the combination of simple electron microscopy and *in vitro* complementation led to the understanding of how a structurally complex particle is assembled from many different components.

It was the success of this genetic approach that led several molecular biologists in the 1960s to try to apply it to more complex biological processes. The burgeoning industries of yeast, *Caenorhabditis*, *Drosophila* and *Arabidopsis* genetics and biological research stem from those initiatives. The injunction was: find mutants and study them as deeply as you can.

Of course, when cloning and sequencing came along in the mid 1970s, all of these fields experienced a revolutionary change, because these were exactly the tools we needed to get to grips with the molecular basis of the mutant dysfunction, and the new and the old genetics flowed seamlessly into each other. When we come to humans or, for that matter, other vertebrates, we have relatively little in the way of an experimental genetic resource. There are some useful mouse mutants and human genetic diseases, and these are under intensive study. The most profound sources of mutant genes are those found in naturally occurring cancer cells, and the study of these combined with biochemical analyses have led to extensive knowledge of growth control and DNA repair in mammalian cells. But still the genetic approach is severely hampered.

Reverse genetics has been proposed as a solution. In normal genetics we have the phenotype and we then look for the gene; in reverse genetics, we have the gene but not the phenotype, so we find what that is by mutating the gene. But this really does not help, except to connect genes and phenotype, although, of course, it can and should be used to test hypotheses about function.

The only way out is through biochemistry of one kind or another. In 1990, I made the remark that biochemistry and communism seemed to have disappeared in that year. Most people thought I said this with glee, but in fact it was with regret, at least for biochemistry. There is another subject that disappeared a few decades ago which we also need to reinvent, and that is physiology. Classical physiology was concerned with the functions of organisms and we are now grappling with the physiology of the cell. In the 1930s R. Goldschmidt wrote a book on Physiological Genetics: what we need today is the modern text. I have also frequently heard it said that what we now need to do is integrative biology; that we are very good at working out how simple systems with few components work but very bad at putting the parts of multi-component systems together. For the latter, I believe we are going to need two things. After all, the machinery of the cell performs the integration of all its component functions, so that cells can display integrated behaviour. So the first requirement will be for a theoretical framework in which to embed all of the detailed knowledge we have accumulated, to allow us to compute outcomes of the complex interactions and to start to understand the dynamics of the system. The second will be the ability to make parallel measurements of the behaviour of many components during the execution by the cell of an integrated action in order to test whether the theory is right. Is there some other approach? If I knew it, I would be doing it, and not writing about the problem.

All the world's a lab ... into a Director

Dear Willie,

Belated congratulations on your appointment as the President and Research Director of the Stoneman Research Institute; I know this happened some time ago and I should have written then, but I now have so little to do that there doesn't seem to be much point in doing anything, even if I can remember to do it. No doubt you have already discovered that being the head of a large organization isn't all that it is cracked up to be, and that it is quite difficult to realize your plans. The problem is that most scientists only think about the next week, and, while you may be lucky to have a few people who are worried about the next three months, you are probably the only one who is looking five years ahead.

Actually, the very fact that someone like you has been appointed is a good sign that change is desired. Research institutes still have a feudal structure and all that the barons generally want is to be left alone. They prefer a king who is neutral; not totally passive, but active enough to go out and get things for them. They want no change and, in particular, they want nothing new and they will argue, like those in a lifeboat amidst drowning survivors, that no more should be taken on board, because the lifeboat will sink and everybody will die. As you will recognize, the only way out of this dilemma is to start another lifeboat. When you get tired of arguing with your senior colleagues you should have a talk with the person who looks after the refectory. You will find a refreshingly different view of the future, which is that you should get rid of all the scientists and their messy ways and turn the place into a first class restaurant and conference centre.

It is inevitable that you will have to make some unpleasant decisions in your career. You can't be nice to everybody because then you would make no decisions at all and would get the reputation of a ditherer. If the unpleasant decisions are seen to be coming from you, you will be seen as a despot, and if you try to make them by consensus, nothing will ever happen. You could try taking the decisions yourself but having them announced by somebody else, like an administrator, who is going to be disliked anyway. My only real advice is that you should be consistent and just. You are only a window through which the people above you, who fund the institute and those below you, who work there, can look at each other. So it is best to keep the window shut and the blinds drawn. It will take about seven years for the blinds to open, allowing the two parties to make grimaces at each other. That will be the time for you to go and you should act quickly before the window is broken and both sides are using you to insult each other.

There are more sophisticated problems that you will encounter and for which some advice may be helpful. One of these is correspondence with cranks and crackpots. You are bound to get letters telling you about the influence of the red shift on DNA unwinding, and so forth. Keep the letters, and when you find two correspondents with similar interests, put them in touch with other. They will be overjoyed and you will have got rid of two streams of correspondence. Open envelopes carefully, and keep them, too, as they can later be used to resolve difficult problems. For example, you can replace the letter in the envelope, reseal it and stamp it "Addressee deceased. Return to sender". Or, suppose you receive a letter from a colleague who requests some probes or, indeed, wants you to do something for him. The tendency is not to reply but to let the letter languish in a tray because it is not easy to refuse the request outright. Then, some weeks or months later, you need something from your colleague. What you do is replace the letter in the envelope, dip it in oil and salty water and send it to a friend in South Africa, say, with instructions to return it with a note beginning: "Dear Sir, while walking on the beach at Isipingo, I picked up this letter ....."

You wait a while and then write to your colleague: "Dear Joe, I haven't heard from you for some time, but would you be able ...." You will receive an excited reply: "Dear Willie, You will never believe this, but...." happily acceding to your request and, with a bit of luck, forgetting about his own. With a lot of friends, many variations are possible. "While climbing in the Andes, I found this letter in a condor's nest" or "While operating on a patient in Kuala Lumpur Hospital, I found this letter in his abdomen". Best of all, with a friend in NASA, is "While walking on the surface of the moon...."

As you can see, this is also the best example of the perfect practical joke, where everybody wins and there are no victims. You will need such tangential sections of reality to make life tolerable. Please let me know of your progress and watch out for that window in seven years time.

Yours ever

Uncle Syd

Loose ends

by Sydney Brenner

As we are all coming to learn, any old list of publications is just not good enough when looking for a job or applying for grants. Candidates' publications are now subjected to microscopic scrutiny but unfortunately not for their scientific content. What is looked for is with whom you write papers and where these are finally published. Today, God would never get a research grant. One member of the committee would deny it on the grounds that the work had been done a long time ago; a second would confirm this by noting that it had never been repeated. Rejection would be clinched by a third member pointing out that, to top it all, the work was published in an unrefereed journal.

I now see many lists where the papers are divided into those published in refereed journals, followed by reviews, abstracts, meetings proceedings, etc. In the old days, neither abstracts nor meetings proceedings were even mentioned, and reviews were included only if they contained an original way of looking at the subject. The best publication list I have ever seen was that of a candidate for some official post who was engaged in defence research. The first two papers were: *Landing aeroplanes on aircraft carriers I & II, Restricted circulation.* The remaining items, numbered 3 to 9, were labelled "Secret". I would have been tempted to inflate the list of secret publications to 19.

The position of your name in the list of authors is very important. Most people seem to go from being the first author on a paper to the last author, without ever writing one by themselves, much as it was said of someone that he went from being a promising young man to a distinguished old man without ever passing through the age of accomplishment. I note a change in the last few years, with the senior author's name appearing increasingly at the head of the list. This should be done only if you are well known, as it carries the risk of you being labelled a recently graduated research student.

The journal in which the paper is published is perhaps the most significant. I have heard seriously discussed that a scoring system should be introduced so that papers in, shall we say, The *Oklahoma Journal of Poultry Engineering* would get 10 points whereas those in *Nature Chicken Genetics* would get 1. I hasten to add that here we would be looking for low-scoring candidates. This would make life simpler for busy committee members but something analogous to vintages would also need to be introduced. Was 1972 a better year than 1989? The most alarming development is that citation rating seems to be taken very seriously. We all know that the most cited papers are those that contain a widely used recipe or method. There is also good evidence that most authors citing the paper have never actually read it but simply copied it from the references of another paper. I once went to look up one such paper and could not find it, because a mutation had occurred in the page number at one point in a readily traceable lineage.

A particularly ludicrous example of futile citation analysis may be found in *Current Contents* of December 5 1994, where the precursors of modern structural biology are purported to be traced by the author, Eugene Garfield, who invented this type of analysis. By following citations from a starting group of papers that have structural biology as a keyword he produces a list of the 17 "core papers in the field of structural biology" among those that were the most frequently quoted during the period of 1981–1993. There is also a matrix of co-citation frequencies which is supposed to reveal the "hidden structure" of this field, in terms of its connections to immunology, biochemistry, molecular genetics, and so on.

Now, if you know something about the field and the contents of the papers, the structure is by no means hidden but obvious. A couple of the 17 "core" cited papers deal with methods of analysis. A few others describe the determination of new macromolecular structures or of sequences that suggest the occurrence of structural domains. You will understandably find references to zinc fingers and to leucine zippers and, not surprisingly, an analysis of co-citation frequencies among the 17 papers shows that the pair of papers most frequently co-cited happen to be the two on zinc fingers. Most of the remaining papers are simply references from the immunological or biochemical literature to proteins that were being studied during the period, such as lymphokines or proteins involved in gene regulation. Much the same is true of the supplementary list of additional highly cited core papers given in the article. And, whereas I can understand how these kind of papers come to be included, given the method of compiling the list, by no stretch of the imagination can most of them reasonably be considered to be the most important "precursors of modern structural biology".

Before we develop a pseudoscience of citation analysis, we should remind ourselves that what matters absolutely is the scientific content of a paper and that nothing will substitute for either knowing it or reading it. We should also recognize that citation often tells us more about the sociology of science than about the science itself. In rapidly developing subjects, the lifetime of the average paper is exceedingly short, perhaps only months, before it utterly vanishes, never to be referred to again. I have been told that in physics only a handful of papers more than 25 years old are still being cited. It must be very gratifying to have a paper in this class, but better still is to be the author of work that is so well known that it doesn't require a literature citation. If in writing a paper now on DNA one cited Watson and Crick (1953) it would probably be regarded as part of an elaborate joke.

All the world's a lab ... last scene of all

Dear Willie,

I was very sorry to have missed your retirement party but my doctors forbade me to travel. Yesterday, I watched the video you sent me of the symposium and the speeches at the dinner; it was a most impressive occasion. I best enjoyed young Ben, my great-grandson, who read my paper for me. I had totally forgotten about those experiments and I hope you didn't mind my using your symposium to make them public.

Now that the singing and dancing are over, you will no doubt be considering what you are going to do with all your newly found free time. Like everybody else, you have probably for long been accumulating a list of the things you are going to do when you retire; all of the places you want to visit, all the books you are going to read, the subjects you are going to learn and the myriad projects you had to set aside because you had no time. Throw the list away. Firstly, you are not going to have all this wonderful free time, because everybody is going to descend on you, with their projects, arguing that now that you do not have a formal job, you will doubtless have all the time in the world to edit their books, or chair their committees or organize their meetings. Unless you are firm, you will find yourself even busier than you were before you retired, except that now you will have no office and no secretary to help you. You must resist all such invitations; don't be tempted to think that this will keep you in the swim of things.

Should you write a book? Publishers will soon be pressing you to write your autobiography, to tell the world how it really all happened. I do enjoy reading autobiographies; it satisfies the voyeur in me — even though there are few torrid scenes to view through the keyhole. Only if you have scandals to divulge, or something very interesting to say, should you write one, because it takes considerable literary powers to communicate the excitement of research. Of course, you are important enough for somebody to write your biography, and perhaps it is better for an outside observer to sing your praises than for you to do it yourself. What about a history of the subject you helped to create or a philosophical treatise on the 'new biology'? There are enough historians and philosophers trying to do this anyway; the history and philosophy of science is an expanding industry and we should not take the bread out of the mouths of the hungry.

You could, of course, go on doing science. You need money for this but quite often it can be arranged. Try to find a patron, because none of the granting agencies will want to help you; in their view you have already had your share, and the money is needed for others. You will want to find a topic that nobody else is working on and the scale of the research has to be small, marginally above pottering about. If you are successful, the project will be taken over. If you fail, it doesn't really matter, as long as the problem was worthwhile.

Or try becoming an inventor as I did when I retired. Most of my inventions are closely guarded secrets. I mean, God never patented evolution, he just kept it a trade secret. My inventions are mainly not practical things or gadgets, but deep theories about everything, from the mundane to the celestial, and from the sublime to the ridiculous. Arguably, my best invention concerns the Complete Theory of the Inverted Telephone Call, now communicated to you and, if our correspondence is ever published, to the world for the first time.

As you know, when a telephone call is made its polarity is taken for granted; somebody is calling and somebody is receiving. How can this polarity be inverted? There is a simple form of inversion, well known to undergraduate students. You telephone your professor at 2 a.m. He answers, usually with burbling noises. You immediately say "Whom do you wish to speak to?" More noises — "What? what?" You then say " I'm sorry, you have the wrong number", and you put the phone down, leaving him perplexed. For years I believed there was a complementary ploy, and in retirement I discovered it. When your telephone rings, you lift it and instantly say "May I please speak to Susie?" Usually there is a stunned silence but sometimes spluttering noises may be heard. You then say "I am terribly sorry, I must have the wrong number", and immediately replace the receiver, leaving the caller confused and puzzled. As this completes my theory, I am now working on a theory of acupunture, which proposes that the needles were once used to test for the levels of anaesthesia; when the pharmacology was lost and the drugs no longer used, it came to be believed that the needles induced the anaesthesia. Follow my lead, and invent some theories for yourself.

I hear my nurse approaching. Please visit me here in Schloss Alzheimer so I can tell you more about these wonderful inventions.

Yours ever

Uncle Syd

Loose ends

by Sydney Brenner

Memory has always attracted me as a fascinating subject. It can be easily studied by every scientist because each of us is at the same time both investigator and subject. When I was younger I had a prodigious memory of which I was very proud. I knew all of the *rII* mutants of bacteriophage T4 and I could tell you where they mapped and all of their properties as well. An old habit of mine was to scan the journals in the library when they arrived. I easily committed all their Tables of Contents to memory and so I could always tell others about interesting papers that had appeared in the last three months or so. Of course, there were fewer journals then and they were much thinner, so perhaps this was not as difficult as it would be today, when one can barely remember where one put the Xerox copies of the papers that one has yet to read.

I first knew that something had gone wrong with my storage system when I found myself inventing papers in whose existence I had total faith. I would say that there is an interesting paper on 6-methyladenine in protozoa in the recent *JBC*; we would proceed to the library where we would, with confident nonchalance, turn to the page, only to find nothing like it there. Nor was the presumed paper to be found anywhere in that or even several previous issues. Sometimes, I would discover the real paper but it was about 6-methylcytosine in algae, not protozoa, and it appeared in a totally different journal. But, more and more frequently these papers stay in the Journal of Imagined Biology; I am still searching for a paper on serotonin which I swear was published in 1972 in *BBA*, starting on a right hand page.

As is well known, names are early casualties of a decaying memory. In the filing cabinet of my mind, many of the tags on the folders are gone but, fortunately, I know what is inside, even though I cannot remember what to call it. There is a difference between reference and object — between saying "My name is Sydney Brenner" and "I am Sydney Brenner" — I know who I am but not what I am called. When holes appear in memory sometimes a deep search can retrieve them by amazing routes. I was once asked who discovered interferon. "E.P. Abraham", I confidently replied, but immediately realized that this was wrong; he discovered cephalosporin. After several hours of turning the cogwheels of cogitation, the correct name of Alick Isaacs emerged. The path had been found, and both it and the first slip were the result of having had the Old Testament thoroughly drummed into my head as a young boy.

It seems now to be accepted that memory is stored in our brains in cellular networks, but there was a time in the 1950s and 1960s when some people believed that it would be stored at the molecular level, encoded in nucleic acid or protein. Once the genetic code had been elucidated an analogy between that and the neural code was often suggested and comparisons were also made between the immune system and neural memory. But the astonishing thing was the number of experiments that claimed to transfer memory or learnt behaviour by means of brain extracts. The flatworm, *Planaria*, was a favourite experimental subject because after one removed the brain of one *Planaria*, to be processed and transferred to another, the original animal would regenerate a new, naive brain, ready for further experimentation.

Most of the experiments were carried out with laboratory rodents: extracts of the sophisticated brains of animals taught to turn left in a maze, for example, were able to communicate this propensity to naive animals once they had received the extracts by intracerebral injection. I remember Francis Crick asking one of the proponents of this research whether the extract could be titrated: his reply was that it took the extract of three trained brains to convert one naive one. Seymour Benzer and I, in a joint lecture at Berkeley, conceived the idea of replacing university teaching by cannibal feasts; in our imagined future, the process of eduction, as we called it, had naturally become so highly developed that one professor was enough for several hundred students.

The favourite active principle in these extracts was RNA, as behavioural transfer was destroyed by ribonuclease. However, as those experiments multiplied and diversified, proteins were accused and found guilty, and I think the field vanished in a flurry of peptides that could transmit fear to rats. It is hard to explain why people wanted a molecular encoding of experience. It had been shown that new protein and RNA synthesis is necessary for the establishment of long term memory, but it is still a big step from there to assuming that experience is encoded in RNA.

The big problem, of course, is how memory is put in and how it can be retrieved. In the immune system, the input is directly at the molecular level and retrieval in the form of an antibody equally involves a molecule. In the brain, a process at the level of cells is required and whereas sequence information can be converted into cellular network, as when genes are used to build nervous systems in development, the opposite path seems most unlikely. Indeed, it seems likely that the only storage of neural memory in molecules is in genes, which need to construct brains to retrieve a species memory.

Now that I think of it, I'm certain that I once saw an important paper on this subject but, alas, I have forgotten the authors' names, the title of the paper and the name of the journal.

Loose ends

Molecular biology by numbers ..... one

by Sydney Brenner

Classical geneticists considered the gene to be one indivisible unit of mutation, recombination and function. The picture was that of beads on string, with recombination taking place between the beads, and mutations creating altered bead states or alleles with different functions. How genes worked was a mystery, but the one gene–one enzyme hypothesis formulated by Beadle made the correct connection — although as late as 1954 there were still people who thought that genes could make carbohydrates or even phospholipids. The unitary hypothesis began to show cracks even before the discovery of the structure of DNA, when rare recombination events had been found between mutations in what was thought to be one gene. These had to be called pseudoalleles and there were even dark hints of the existence of subgenes.

It was Seymour Benzer's work on the fine-structure genetics of the *rII* locus in bacteriophage T4 that destroyed the classical model of the gene. He showed that each gene, defined as a functional unit, contained hundreds of mutational sites that could be separated by recombination. A simple calculation revealed that this map was on a scale that corresponded to individual base-pairs of DNA.

To mark this new view of the gene, Seymour invented new terms for the now different units of mutation, recombination and function. As he was a physicist, he modelled his terms on those of physics and just as electrons, protons and neutrons replaced the once indivisible atom, so genes came to be composed of mutons, recons and cistrons. The the unit of function, the cistron, was based on the *cis–trans* complementation test, of which only the *trans* part is usually done.

Of these terms, only cistron came to be widely used. It is conjectured that the other two, the muton and the recon, disappeared because Seymour failed to follow the first rule for inventing new words, which is to check what they may mean in other languages. In his case it was French that did him in; muton is far too close to the word for sheep, and recon can be confused with an insult used by taxi drivers in Paris. Incidentally, I was told of another example of this principle in the form of an anti-freeze spray used on car doors in the winter in Finland that had a name very much like Piss.

Seymour's pioneering invention of units was followed by a spate of other new names, not all of which will survive. One that seems to have taken root is codon, which I invented in 1957; and the terms intron and exon, coined by Walter Gilbert, are certain to survive as well. Operon is moot; it is still frequently used in prokaryotic genetics, but as the weight of research shifts to eukaryotes, which do not have such units of regulation, it may be lost. Replicon, invented by Francis Jacob and myself in 1962, seems also to have survived, despite the fact that we paid insufficient attention to how it sounded in other languages. This struck me forcibly some years later when a Japanese colleague asked me what I thought about the leprechaun hypothesis.

Units are needed in science whenever measurements are made. Physics has dozens of them named after physicists. There are Ångstroms, newtons, joules, einsteins, debyes, curies, and so on. We have svedbergs in biology, but sedimentation constants are still close to physics. There is, of course, the centimorgan for the measure of recombination, but I think we could do with more. Perhaps we should get rid of kilobases and substitute kilowatsons, and substitute crick for triplet. We could then say that the human genome has 3 000 megawatsons (or 3 gigawatsons) of DNA, and the average coding sequence in eukaryotes is 410 cricks long. And, of course, for those of us who study evolution, one million years must be called a darwin.

I have used the word quit as the logarithmic unit of sequence information. Thus, a bacterium with 4 megawatsons of DNA could be said be contain 11 quits of sequence information ($4 \times 10^6 = 4^{11}$). The careful reader will notice that one quit equals two bits, and that the human genome, with 16 quits of sequence information, makes the human a 32-bit animal.

I have been struck by the fact there is no unit for the unit. I am an assiduous collector of errata, and I recently found a gem tucked away in a corner of *Nature*, urging the reader to substitute the words "500 micrograms" for "500" and "25 millilitres" for "25" in what must have been a mysterious paper. At the time, I also realized that this provided a wonderful way to delay the work of one's scientific competitors. Just imagine the erratum that says for "kilograms" read "micrograms". I had thought that these and related problems could be solved if we had a special word for the unit itself. I toyed with the idea of using cantor or piano, or even frege, from the realms of the theory of arithmetic, and it took me some time to realise that we had a better one closer to hand. I therefore propose that we use the word monod as the unit for the unit. Instead of saying 125 millilitres we would say 25 millimonods of litres; and instead of 128 nanoseconds we would say 128 nanomonods of seconds.

Sadly I have just discovered that the word monod is easily confused with the word for idiot in a Sudanese dialect, so this will not work.

I have always been amused by the term scientific integrity, because I would have thought that each part of it implies the other. I understand, however, that it is used so that breaches of scientific integrity — scientific fraud — can be distinguished from ordinary criminal offences, such as embezzling research funds or stealing money from the lab coffee club. Scientific fraud seems to be on the increase but whether this is because there are more scientific criminals or more efficient ways of discovering fraud is totally unclear. I suspect that there is, indeed, more fraud, but only because there are more scientists alive than ever before, and that we hear more about it because the scientific weeklies are increasingly active in bringing fraud to the attention of their readers, who love reading how cold fusion can land one in hot water.

I have for long made a special study of scientific fraud (in theory, only, of course) and have concluded that, like the seven types of Empsonian ambiguity, there are seven types of scientific criminality. We can begin by disposing of the first two, which are obvious and boring. Plain plagiarism — that is copying somebody else's paper — and plain fraud — that is inventing data — are easily detected, and usually committed by lazy and stupid people who shouldn't be doing science anyway. The only such person who is hard to detect is the one who publishes accounts of obscure non-existent Congolese insects, in obscure Estonian journals, but then he isn't getting much gain for his criminal activity. Word processors allow for easy cutting and pasting and I have found many papers that contain rearrangements of previous papers by the same authors. But self-plagiarism is not yet thought to be a crime.

The third type of crime is petty deception, and one to which we can all plead guilty. It consists, for example, of leaving out one point on a graph, because it falls off the straight line, and ascribing this to bad data produced by dirty tubes, pipetting errors, etc. This is not thought improper but the effective exercise of scientific discrimination. But it could in some cases lead to a crime. The fourth type depends on a form of self-delusion and usually involves making a set of tricky observations, like counting scintillations or watching cells move about. The individual unconsciously learns how to select runs of data that fit the theory. What is interesting is that other people can learn to do this as well and the phenomena can then achieve specious reproducibility. Related to these is the fifth crime — that of over-decoration. It consists of "improving" the data by, for example, amplifying the scale of the experiment. For instance, suppose an experiment using 500 petri dishes shows 0 on the control and 3 in the experimental group; if one claims, instead, that one used 50 000 petri dishes, these figures become 0 and 300, which certainly looks much better. You would be able to detect such a crime by showing that there was not enough money in the grant to pay for so many dishes.

The sixth type of laboratory crime is the most common. It is co-operative, involving two people in a hierarchical relationship. The junior person at the bench makes an innocent mistake or falls victim to one of those statistical fluctuations that one finds in many experiments. The result is taken to the supervisor, who, instead of suspecting an entropic intrusion, leaps to the conclusion that this is the discovery of the decade, showing that some phenomenon, like self-replication of carbohydrates, exists after all. Instead of urging the junior colleague to do the experiment in a different way with other controls, he announces that if X were carried out then Y should ensue if the theory is correct. Back at the bench, what happens is not precisely Y but something that, with slight adjustment, can be made to look like Y. After a few cycles of this interaction, the senior colleague comes to believe that his genius cannot be denied; the junior is now hooked and cannot go back, and what starts as a little massage will end up as a total invention of results. This is not fraud but embezzlement because it is like the man who works in a bank and takes money each week to bet on the horses adjusting his books accordingly. Each week he bets more and more, believing that one day his horse will come in and he will be able to put everything back before the auditors turn up. Alas, the horse never wins, and the auditors do find out. The biggest problem in such cases is to get the senior person to admit to himself that he was wrong.

The seventh and last type of laboratory crime is also co-operative, and has very distinctive features. The work culminates in a paper reporting a new and unexpected phenomenon, supported by a wealth of detailed experimental results. The research is usually in a very active field, where, if wrong, it will be discovered in a few weeks. We therefore cannot account for this as simple fraud, and it must be viewed as a form of schizophrenia, the junior perpetrator believing that he has a special way of penetrating Nature to discover the truth directly. To him, experiments, graphs and tables are simply conventions that need to be followed to make his insights public and he often constructs these faultlessly. He believes that anybody repeating the experiments will get the same results because these are logical deductions from discovered truth.

The role of the senior person is different in these two types of co-operative crimes. In the first, he is an active partner, taking advantage of his junior's naivety; in the second, he is a passive but willing dupe, blinded by his junior's cleverness. In both, he is guilty of not exercising critical judgement and of letting all kinds of other motives get the better of him. So the next time somebody brings you a strange result, try not to say: "But that means.....". Just send him back to the lab to test the pH of the distilled water or to make sure there are no bacteria growing in the buffer. You could, in this way, avoid the start of a most unhappy relationship.

Loose ends

by Sydney Brenner

Molecular biology by numbers ..... two

Two is the fundamental number for genetics; all of us are the products of single zygotic events but the zygote is formed from two gametes, and two different sets of chromosomes make up our genomes. When I first learnt genetics, it was about diploids, and meiosis and the generation of haploid gametes was central to its understanding. Incidentally, lacking a classical education, I thought haplo came from some Greek word meaning half, and, of course, half of two is one, so I thought they could have called it monoploid. Later I discovered that haplo does come from a Greek word, but it means single or simple.

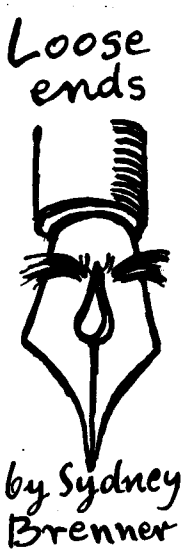
Those of us who entered bacteriophage genetics with a biological background had to unlearn all the genetics we knew and adapt to the genetics of organisms with single (haploid) genomes. The physicists, knowing no biology, had a much easier time. At that time, there were strong doubts that viruses could be said to have any genetics at all, and Delbrück even ascribed genetic exchange between phages to some kind of directed mutation. Hershey got it right and called it recombination. Much the same confusion bedevilled early bacterial genetics, but with the discovery of Hfr strains and the elucidation of the mechanisms of genetic exchange by Hayes and Wollman and Jacob, *E. coli* not only had genetics but sex as well. We had males, females and mating; there were zygotes and segregants.There were in fact diploids, but these were incomplete and temporary. Later, with episomes, true diploids could be constructed and *E. coli* genetics did begin to look more and more like the old genetics we had all forgotten. There were geneticists working with yeast and *Neurospora* with well studied sexual cycles, but the diploid phase was only a brief stage in the life histories of these organisms and could be safely ignored. Generations of students came to learn genetics through haploid organisms, and terms such as leptotene, meiosis, gametes and polar bodies disappeared.

Then we all turned to higher organisms and everybody had to learn diploid genetics and come to terms with heterozygotes and the difficulties of finding recessive mutants. Fortunately, I alighted on *Caenorhabditis elegans*, which is a self-fertilizing hermaphrodite with rare males, essentially giving all the benefits of haploid genetics in a diploid organism. The fact that it is driven to homozygosity makes it sensible to talk about a single genome structure in the same way as we can talk about the single genome of yeast or *E. coli*. Nowadays, with techniques of DNA cloning and transgenesis, we can do the genetics of almost everything and we are no longer bound by the tyranny of life cycles.

Many years ago, when the late David Marr joined our group in Cambridge, we began to think about theoretical and computational biology between sessions of struggling with a computer and gluing pieces of paper tape together. One of the mathematicians who had attached himself to our group wrote a paper on population growth of theoretical organisms with more than two sexes. Quite apart from some ribald speculation on the anatomy, physiology and ethology of the reproductive process, we had to be concerned with the chromosomes and how sex would be determined. For $n = 3$ sexes, the organisms need to be triploids, with reduction to haploids in each case and with the triploid genome reconstructed in one act of conjugation. When n is large, say 15, there needs to be some kind of orgy. There are of course alternatives: the three-sex organisms could be tetraploids and produce one diploid and two haploid gametes; then, in sex 1, only the diploids survive, in sexes 2 and 3, only one of the haploids survives. We can imagine sequential mating as well, and, of course, if we have parthenogenesis and hemaphroditism too, the possibilities become very large. The exercise for five sexes is left to the reader but regrettably implementation must await the genetic engineer of 2053.

Two is also the important number for molecular genetics. The double helix, with its base pairs and its two inventors, Watson and Crick, is an icon permanently embodying this number. The structure incorporates the notion of two-fold symmetry with the dyad at the side, perpendicular to the long axis of the molecule. It is hard to explain rotational symmetry with our bodies, and hand-waving will not do because we have the wrong kind of hands. Our hands are bilaterally (mirror) symmetrical and we need two hands of the same kind, that is, two people. A handshake is exactly right, and one should avoid drawing triangles or squares to illustrate symmetry. I once wanted to test whether students who could give a perfect text-book description of DNA really understood it, so I asked two questions. One was: a base pair is removed from DNA; in how many ways can it be replaced? Most answered one, but the correct answer is two; the way you took it out, and turned over. The second question did not have much to do with symmetry but was: what lies between the bases? I got all kinds of answers — air, water, electrons, vacuum and so on. The correct answer is nothing: the bases are 3.3 Å thick and the students had been misled by models which used flat metal plates to depict the bases. I sent them off to read a paper on the crystal structure of anthracene.

In most traditions, the number two implies discord, division and disunity, as may be seen in such words as doubt (Zweifel in German) and duplicity. Two has always been seen as reflecting the breakup of some primordial unity. In biology, two is the only way by which a new unity can appear and it gives rise to constant renewal. We can say: two be or (in the haploid case) not two be.



I am a compulsive bookshop browser and have spent many happy hours learning all manner of things from books I could never afford to own. I particularly like reference books — dictionaries, etymologies and collections of quotations and euphemisms. It is in bookshops that I have discovered that nearly all my ingenious theories of word origins are totally wrong, and I am now planning to be the would-be author of a should-be etymology.

The other day, while nonchalantly paging through the index of a rather expensive new book on humorous quotations, I was pleasantly surprised to find my name. Hastily I turned to the page indicated. Was it 'He was a man of slender ends' or, perhaps 'To go tongue in hand'? No. It was some remark I had made about computers being poised between the obsolete and the non-existent.

Actually, I made this remark about buying a computer. It is now nearly thirty years ago that I found myself trying to acquire a research computer to help us in the reconstruction of the nematode nervous system. I discovered that only two kinds of machine were available. There was one I could have immediately, but it was obsolete, small and slow — really a pile of junk. The other was a wonderful machine, bigger and faster with a radically new design, which was actually being built at that very moment and which I could have in six months time.

I realized that this choice between the obsolete and the non-existent would always be there, because in six months or a year's time, the same would be true; last year's non-existent machine would materialize into instant obsolescence and there would be a better one to wait for. My conclusion was that if we followed this logic, we would never buy a computer. Instead, we bought one which had just appeared and occupied a metastable state between reality and the dream. It was a marvellous British invention and the exact opposite of user-friendly. It found all users most distasteful and seemed to go out of its way to avoid any constructive interaction with us. Most of the time it responded by going absolutely silent; at other times it issued cryptic remarks before collapsing completely. As was typical of such advanced machines at the time, there was very little software; there was only an assembler and programs were written and punched on paper tape for entry into the machine. Our paper tape reader sometimes had outbursts of hysterical rage and the tape would emerge neatly shredded into several strands. We wondered whether the reader had been developed under contract to some intelligence organization and we had unluckily been delivered one of the top secret models.

As I am wont to repeat to my younger colleagues, this was the real way to learn about computing. I had found a description of a string processing language called TRAC in a journal and I decided to write an interpreter for the machine we had purchased. I reasoned that I could then free myself from the bonds of assembly language and write all my programs in the TRAC language. I managed to do this and indeed the first program ever to compare nucleic acid sequences was written in TRAC. It was used to look first at tRNAs and later at longer sequences. The most difficult part of the program was that needed to print the comparisons in panels on a teletype machine.

John White was my teacher and he and I, together with David Marr, wrote a large amount of system software for this machine. I had become so skilled at assembly language programming that I didn't think twice about altering a Fortran compiler to use with our disc operating system. We also invented and built several gadgets, such as a cheap digitizing plate and a wonderful machine to handle electron micrograph plates for comparisons. All of this work became valueless when the machine — by then slow, small and obsolete — was junked and its pieces given to other people who could use them. My TRAC became useless, as the interpreter had gone with its unique host. I resolved never to become so involved with computers again, but I knew they were going to be essential tools in biology.

Growing up with crystallographers really set the stage for our computing interests, which went beyond sheer number crunching. But most biologists thought all of this was a waste of time and all biochemists were convinced that computing was just an excuse to get off doing work at the bench. I spent many hours persuading people that computing was not only going to be the essential tool for biological research but would also provide models for analyzing complexity.

The development of sequencing techniques and their widespread application has generated enormous databases of information, and the need for computers is no longer questioned. The amazing progress made in computers themselves and software for them, means that very powerful models are widely available at low cost. There is no inflation for computer expenditure; one spends the same amount each year but every two years or so one gets three times more for it. With the development of computer networks, everybody will be in permanent communication with everybody else, all playing in the same gigaband.

All except me. Some years ago, when I took up computing again, I decided to do better than the first time around. So I learnt the C language and wrote an interpreter for TRAC in C. I have a large suite of programs written in an even flashier TRAC language that I use to study sequences. I can run these programs on any machine that has a C compiler that can compile the interpreter. I have my private language that I doubt anybody else will want to learn. But I am no longer trapped in one machine and I can work happily with my Mac or with the most powerful, multi-this and multi-that supercomputer available.

Loose ends

by Sydney Brenner

Molecular biology by numbers ..... three

Three nucleotides correspond to each amino acid in the genetic code and triplets were thought to be the coding ratio from the very early days. The key to all the work was to define the *proper* amino acids — that is, those found in proteins — and exclude all the others. In the 1950s, textbooks of biochemistry, vying with each other for the length of the list of amino acids they could produce, included both cysteine and cystine, citrulline, ornithine and even *D*-amino acids, β-alanine and hydroxy-proline. Getting the twenty was the fundamental step. Francis Crick and Jim Watson wrote them down and I got to that number from the fragments of peptide sequences being accumulated by Fred Sanger and others. Three nucleotides was the minimum that could be used to get twenty, although there was a suggestion, which Francis called the 'naive biochemist's code', that sixteen of the twenty amino acids were coded by doublets and the remaining four by singlets. (This has an echo in a phrase I often use — 'the naive molecular biologist's gene', which is almost exactly one kilobase long because NMBs believe that all proteins are exactly 333 amino acids long.)

What made the early days of genetic cryptography difficult was the self-imposed stereochemical constraint. The 3.3 Å repeat of nucleic acids is about the same as the 3.5 Å chemical repeat of the polypeptide chain, and it was thought that this one-to-one physical correspondence was necessary for the mechanism of protein synthesis. Maintaining a coding ratio of three nucleotides and a step size of one nucleotide for each amino acid requires special solutions which were first clearly stated in Gamow's 'diamond' code. This was the first of the overlapping triplet codes, in which, in a nucleic acid string, nucleotides 1,2 and 3 code for the first amino acid, nucleotides 2,3 and 4 code for the second and so on. The diamond code was degenerate in the sense that more than one triplet corresponded to a particular amino acid; some had four, and others, two. The particular decomposition was obtained by the application of a rule based on totally implausible and unrealistic physical assumptions.

Gamow's particular code could be disproved for the known protein sequences, but it had already become clear that there were many ways of degenerating the triplets and, being biology, it could have been an accident of evolution and quite arbitrary, rather than being derived from some elegant mathematical rule. It was not feasible to test all of the codes, one by one, for compatibility with the data. Indeed, there was a paper to show that if we were going to do this by computer we needed one several orders of magnitude more powerful than those available at the time and that we should have started the work at the onset of the fall of the Roman Empire.

I realized that all overlapping triplet codes had one thing in common, regardless of the degeneracy. Because a dipeptide would be coded by four bases, the codes all constrained the number of possible dipeptides to 256, rather than the 400 that are the maximum number of dipeptides possible from 20 amino acids. There were insufficient data to test this prediction directly but by the autumn of 1954 I had statistical evidence that the known dipeptide occurrences fitted a Poisson distribution based on 400 rather than 256. I showed my chart to Gamow who promptly lifted it and put it in a review he was writing with a footnote acknowledging that I had done it as well. Coding was therefore not only my first sally into theoretical biology but also my first encounter with conduct in modern science. Shortly thereafter, I found the proof that all overlapping triplet codes were impossible and this led to the sterochemical constraint of one nucleotide – one amino acid being discarded. I proposed what I privately called the 'Humpty-Dumpty' theory of protein synthesis, which was that it begins at the beginning, goes on until it reaches the end and then stops. When Francis proposed the 'adapter hypothesis' we knew that the code would only be found empirically, not through the exercise of the mind. Theoretical coding died and its most interesting product, the elegant comma-less code, became an historical curiosity.

The other triad in molecular biology is embodied in the 'central dogma', often expressed in Middle Sloganic as DNA makes RNA, RNA makes protein. I have always been slightly puzzled why Francis chose the word 'dogma' as he is the last person to be described as a church man, even of the most liberal and reformed kind. When reverse transcription was discovered, many people gleefully tried to depose the central dogma but, as has been made clear by Francis, the rule really applies to nucleic acid and proteins; that there are two kinds of nucleic acids and ways of going backwards and forwards between them is trivial. The dogma is better and more deeply stated in the diadic form: once information gets out of DNA into protein it cannot go back again. Perhaps it became a triad because if there is a beginning and an end there has to be a middle.

I once formulated the 'central dogma of biotechnology' as DNA makes RNA, RNA makes protein, and protein makes money. For this, I won an exceedingly small prize in Japan and my work was translated into one language. Only later did I realize that I had missed a golden opportunity to increase my compensation. Introducing the fourth component breaks the original dogma and allows closure of the cycle, because money allows information to be taken out of protein and put back into DNA. That is what we are all doing nowadays and, if one wants an anthropic principle in science, this is a much better one than that talked about in cosmology. Money does make the world go round.


Loose ends
by Sydney Brenner
1996

Loose ends

Sydney Brenner

Another year has passed and it has been a quieter one, at least where I am concerned. I received no outraged letters, no threatening faxes and not a single obscene phone call. To my bitter disappointment, people have been quite laudatory. I have even been introduced at a seminar as the author of this column, which makes a difference from being called the 'Father of the Worm' all the time. If there were any exciting scandals last year I can't remember them. Nor have there been great issues for debate — except for the usual ones of how to get money for research and how to get papers published when the work is done. I suspect that electronic publishing has made some progress; judging from my junk mail, one can now get lots of journals on CDs (without musical accompaniment, I am told) and one does not have to wrestle with heavy journals any more.

What I can record is the inexorable advance of paper work, bureaucracy and administration — or, as perhaps I should call it, management. Everybody seems to have gone for the idea; indeed, one of the 'alternative' columnists in this journal recently advocated training in management for young scientists. I get really upset when the young begin to display the signs of creeping conservatism, and I begin to think that the past 20 years have brought about a major change in our culture. We now are invited — and if we decline, compelled — to work and act as though we are running a business. Many people in high places in Britain urge us to adopt the practices of business, and like to think that they will make everything much more efficient if the heads of Research Councils and Universities are called Chief Executives rather than Secretaries or Vice-chancellors.

I predict that very soon every grant application will have to include a strategic mission statement and a business plan, as well as an organogram outlining the structure of the laboratory with a clear definition of who reports to whom. Perhaps as time goes on and science gets more difficult to do, the actual research project will come to be a smaller part of the application. Eventually it may disappear all together. This would fulfil the ultimate dream of every manager and administrator, which is simply to have pure management with no content, with a precise delineation for everybody of how orders flow — that is, from whom do they take them and to whom do they transmit them. Hospitals are moving to this state quite quickly and I am sure there are many who think that everything would function better if they only could get rid of all the patients.

I can offer one word of advice; I have personally found it extremely useful, when dealing with managers, to invert all the catch phrases and exhortations. For example, suggesting the introduction of "pay-related performance" is enough to stall most managers for plenty of time.

It seems very churlish of me to start a new year on this irritated note, but I sense we are getting pushed around more and more by people who don't know anything about science and haven't solved a single problem in their lives. In a more reflective mood, however, I wonder whether this is really like a problem in epidemiology, where one finds it hard to distinguish between a real increase of a disease and the development of better means of diagnosis. Advancing age certainly sharpens one's diagnostic tools but I am sure that there has also been a real increase, and certainly since the fall of the Soviet Union which seems to have released a lot of people from other activities.

While I am about it, let me expose another of my bugbears — security. Everything is now locked up; I carry a bunch of keys like a mediaeval jailer and a whole lot of magnetic cards to get in and out of buildings. And, of course, if anything untoward happens in the laboratory, like a fire alarm going off or somebody staying on to work late, gentlemen dressed in blazers, looking as though they belonged to some sports club, arrive and not only confer amongst themselves but also with somebody called Roger who is at the other end of their walkie-talkies. They seem unable to do anything without Roger's permission, but, inevitably, they will ask you what you are doing in the lab at 2 minutes past 5 o'clock, and they seem nonplussed when you explain that you were trying to clone a gene, or communicate with the editors of a journal, or one of the many things we scientists get up to.

We need to fight back against this onslaught. We all know that one reason that the world is in such a mess is that business men are not very competent themselves. If their practices come into science, we could expect chaos. We could come to have leveraged buyouts of Universities financed by junk bonds, and peer review committees could be replaced by market surveys. Head hunters would find professors, and the heads of laboratories would pay themselves enormous salaries and bonuses for publications in the right journals. We may even have stock options to support the best students and postdocs.

When next you read that management is good for you, or that market forces should determine what we do, then I urge you to stay a young Turk. When the young Turks become old Greeks, it is really time to worry.

Loose ends

Molecular biology by numbers ... four

Sydney Brenner

The tetrahedron has four triangular faces and, because the three-fold axes of symmetry also pass through the four vertices, it is the dual of itself. We know it best as a description of how the four bonds of the carbon atom are disposed in space.

I was once told by a theoretical physicist that the values of the fundamental physical constants need not have been the same during the evolution of the universe, and, of course, this means they could have been different now. This would affect the masses and charges of the particles that make up the atoms and everything could be different. "For example", he said, "carbon might have been trigonal and not tetrahedral and life might not have evolved". "No", I replied "We would have been the same, except that carbon would have been called nitrogen and something else would have been called carbon".

I was then relatively unsophisticated, but now I would tell him about Brenner's first anthropic law of cosmology, which is that every universe will, about half way through its history, evolve a life form called a theoretical physicist to raise doubts and questions about its existence.

When four different groups are attached to carbon we can have two distinct arrangements, which are mirror images. Chemical syntheses produce both forms but only one is found in living systems. I spent many hours of a generally misspent youth teaching myself chemistry and I found this area (now called chirality) the hardest to grasp. It took me a long time to find the difference between D and L on the one hand, and + and –, on the other; D and L describe the disposition of the bonds in relation to the standard forms, D- and L-glyceraldehyde, whereas + and – tell us how solutions rotate plane polarized light. I can remember how pleased I was to find that D(–) was not contradictory.

There have been many attempts to project this molecular asymmetry onto higher levels of structure and function. I can remember reading a paper in which the author thought he could distinguish two different races of *Paramecium* by whether they rotated to the left or to the right when they swam. This could well still be true, but what must be wrong was his theory ascribing this to the enantiomorphic molecules.

Jack Dunitz and I once explored a theory of a universe with mirror symmetry, in an (unwritten) science fiction story about the arrival of a spaceship on Earth. Several centuries earlier, a spaceship had been sent out from Earth to prove that the Universe was finite and, as far as the Earth inhabitants could tell, it was the same spaceship returning. At the celebratory banquet, however, the spaceship crew, who were all believed to be descendants of the original crew became terribly ill. And the same happened to the Earth inhabitants at a return dinner. A clever biochemist then discovered that the visitors had D-amino acids and L-sugars, so that when the original spaceship set out from EARTH a mirror image left HTRAE. Of course, at the mirror they should have collided or, more likely, been reflected back, but this is where we invoked the uncertainty principle and got them past each other.

Recently, Steve Kent actually created a mirror enzyme by synthesizing the protease of HIV out of D-amino acids. It was active only on a mirror substrate — that is, one with D-amino acids. An interesting examination question for advanced students of molecular biology would be to design a simple mirror self-perpetuating system and to say what would have to be synthesized chemically in order to prime it.

Many organisms have bilateral symmetry but this cannot be a true mirror symmetry going down to atomic scale. (If it were so, it would constitute proof of an extreme preformationist theory.) Rather, such bilateral symmetry is epigenetic, arising from a growth pattern that is generated, as all patterns are, from the repeated application of a simple rule in space and time. For organisms, handedness would not go down lower than the level of cells.

Four is also the number of different bases in DNA. We have two base pairs and two ways of having these in DNA. These are not, however, the only mutually orthogonal base pairs possible. There are others such that each member pairs only with its partner and not with any other base. Steve Benner has synthesized such pairs and has shown that they can be accommodated in the DNA structure. They are also functional, in that they will be correctly incorporated by both DNA and RNA polymerases. But, of course, they are meaningless. This suggests more examination questions for our advanced molecular biology students.

All of this goes to show that four was not necessarily the unique number of bases that could have evolved and that the selection of this number was a historical accident, as was the selection of the handedness of the components in living cells. Physicists like everything to follow inexorably from laws of Nature. But biology is very unlike this type of well-ordered state, with its disciplined citizens, and operates rather more like sets of loose and clever gangs living, with mutual respect, in a hazardous and unpredictable landscape.

Loose Ends

Out of Africa

Sydney Brenner

I spent most of December and more than half of January engaged in a series of respiratory infections that seemed to be resistant to all the antibiotics that I could find. I began to have visions of being the first to succumb to a new plague which would finally eliminate humanity.

Years ago, flying in the old propeller-driven aeroplanes, I used to imagine that I could penetrate directly into the intricate machinery and could see the hairline cracks developing on the spinning crankshafts, but I resisted bringing this to the attention of the crew. With the same tele-microscopic eye, I now saw an 18 kilobase plasmid in the bacteria in my bronchi, carrying resistance genes for everymycin, omnicillin and totocycline, with multiple sex factors capable of transferring this lethal ring of DNA to all bacteria and possibly to fungal and other cells too. Actually what I had was 'flu from Europe succeeded by another from Japan and then a third from America. I also suffered a little from what I call justifiable hypochondria, which is that you are better off with the diseases you think you have than the ones you might really get.

In the last week or so in January I returned to South Africa for the first time since a very short visit in 1972, which had been the first since I left in 1956 to go to Cambridge. In Johannesburg everything had changed completely. The old Medical School building was still there but was used for something else. From the outside of the building I identified the windows of the BSc Lab where I began my formal training in science at the beginning of 1944. I also found the windows of the office I shared with Seymour Papert in 1951. It was Seymour who taught me what little mathematics I know; in return, I taught him neurophysiology. He certainly was the better pupil and also probably the better teacher.

Seymour was at that time interested in Group Theory and in something called Lattice Algebra. Although I did go systematically through the elementary algebra of groups, I found that I could not understand it by starting with axioms and going on to prove theorems. The symbols just would not enter my head: and I could only get to grips with it by drawing pictures. I discovered that a matchbox was the best way to understand the non-commutativity of group transformations. Try it for yourself; the application of two successive rotations a and b around two axes has different outcomes depending on the order in which they are done. I came to the conclusion that there were two different ways of doing mathematics: by pictures or by symbols — that is, geometry or algebra. My brain refused to play the symbolic game, so I was a geometer.

Many years later I discussed this with a famous mathematician and found that he agreed. And although his work in the field of algebraic topology was full of the symbolic stuff, he confessed that before he wrote it down formally he drew little diagrams on the side of the paper. Perhaps it is that geometry connects one more with reality than does the abstract form of mathematics. Later I found that computer programming had the same reality-connecting function. As anybody who has done this knows, there is nothing more real than a program that does not work and nothing more satisfying than finding and removing the bugs from it. Speaking of bugs reminds me of a lecture I once attended on supercomputing, where reference was made to an application to the analysis of the texture of fabrics by people in the garment business. My witty neighbour remarked that there the program did not have bugs but moths.

To return to early days in South Africa. The library was my main connection with the outside world. Journals came by sea two to three months after they were published in Europe and America and, of course, during the last years of the war, attention was diverted elsewhere especially in Europe. There were also not so many of them, and they were both much thinner and did not appear so frequently. Editors were also much more polite, I still have one of those wonderful notes that begins "The Editor of *Nature* begs to present his compliments to Dr Sydney Brenner and .....". One did not mind being rejected after being addressed in this way. The pace of science was one or two orders of magnitude slower than it is today, and you could certainly add another order of magnitude for being stranded in South Africa. This sense of isolation, I later found, was shared by the Australian scientists I met when I went to Oxford.

We learnt everything from books and from our friends. Being self-taught has many disadvantages but it is the best experience for doing research. As I have often told students worried about the oral examination for their PhD thesis, they should have no concerns about the thesis itself because they will be the world's expert on their topic. All they have to be worried about is whether the examiner will ask them something outside the thesis, like the chemical structure of water. The important thing about research is that it is new, and is about going where none have gone before, and you have no other recourse but to teach yourself.

Loose ends

Molecular biology by numbers … five

Sydney Brenner

Watson and Crick are famous for the discovery of the double helix but there is a less widely known *Ciba Symposium* paper by Crick and Watson that puts forward a general theory of virus structure based on principles of assembly of subunits. Few people remember that Jim Watson came to Cambridge to work on the X-ray crystallography of tobacco mosaic virus; I suspect that had he not been distracted by DNA and genes he might have become a great force in structural biology.

The argument in the Crick and Watson paper was that if the coats of viruses (now called capsids) are built of identical protein subunits, there would be a limited number of ways of assembling these to produce the regular structures found. Thus helical symmetry, where the subunits are related by a translation and a rotation, would generate rod-shaped viruses. In theory, these could grow to infinite length; Crick and Watson suggested that the fixed length of such viruses is determined by the length of the enclosed RNA molecule. For the assembled subunits of spherical viruses to enclose space, they argued, only three classes of symmetry are possible: 3:2 (as found in the tetrahedron), 4:3:2 (cube or octahedron) and 5:3:2.

They concentrated on the last class, as it provides structures that approximate better to the spherical shells of viruses such as poliovirus. 5:3:2 is the symmetry found in the eicosahedron, which has 20 triangular faces (3-fold symmetry), 30 2-fold edges and 12 vertices through which the 5-fold axes pass. The same symmetry is shown by the dodecahedron, the dual of the eicosahedron, which has 12 pentagonal faces and 20 3-fold vertices. If one placed three subunits on each triangular face of an eicosahedron, they would be related by 5-fold symmetry at each vertex, 3-fold on the faces and 20-fold at the edges, hence 5:3:2. Crick and Watson therefore predicted that spherical virus coats would contain 60 identical protein molecules, or some multiple thereof, because the subunits may themselves be composed of dimers or trimers.

The predictions of Crick and Watson have been completely vindicated by subsequent research on virus structure by electron microscopy and X-ray crystallography methods. The 5-fold way has come to stay. In conversation, I have speculated from time to time that these symmetry elements may be used in cells to build components where only one entity is required. This would circumvent the problem that it is not possible for a cell to produce exactly one protein molecule because regulation of protein synthesis is an inaccurate analogue process. However, if the component were built of 60 subunits, it should be possible for a cell to produce an average of 90 protein molecules, and reliably make more than 60 and less than 120, so as to provide enough for one structural assembly.

Related to this work of Crick and Watson was the discovery by the architect Buckminster Fuller that hexagons can only build plane sheets and space can only be enclosed by adding some pentagons. Actually, Euler proved a long time ago that twelve pentagons are required, but since he is not known to most molecular biologists or architects, he has not received much credit for his work.

In recent years, chemists have been building large molecules out of carbon atoms. When they made C_{60} and found that it had twelve C_5 rings and ten C_6 rings, they named it buckminsterfullerene or, 'bucky balls'. Buckminster Fuller built very large objects that everybody could see from distant photographs, whereas the spherical viruses are very small and one needs a high-powered electron microscope to see them at all. Had the chemists known either some molecular biology or some molecular biologists, we might have had crickwatsene and 'cricky balls' instead. And I would have had to be writing somewhere else to try to change history.

The structure of the virus coat is specified in the virus genome and we can therefore correctly say that it is possible to encode a mathematical rule in DNA, or more simply, DNA can contain instructions for building an eicosahedron. We could say this without knowing too much about the internal machinery just as we say today that DNA specifies brains.

It is instructive to see how 5:3:2 symmetry is written in DNA. It is implicit in the amino acid sequence of the coat protein, because the protein needs to fold up in a particular way so that its surface presents the donor and acceptor sites that specifically interact to generate the 5-, 3- and 2-fold axes. These sites are specified by small regions of nucleotide sequence that are distributed throughout the gene that specifies the protein. We can only point to these patches of DNA when we know about the structure of the protein and the nature of the interactions with itself. Going the other way — that is, deducing the structure of a virus from the DNA sequence alone — would be impossible without knowing the principle of construction which, in this case, is that the gene makes a protein which folds up and assembles with 5:3:2 symmetry.

The lesson is that we have to know a lot about the molecular biology of cells to understand what their genes can do, and that viruses are simple models that provide insights for what will be required to explain higher-order structures in cells.

Loose ends

Out of print

Sydney Brenner

I have spent many hours these past few months listening sympathetically to complaints by quite a few young scientists about their treatment by editors and referees of well-known journals. Since their future careers — jobs, grants, recognition — turns on the issue of publishing in the right journals, they have all the right to be worried and even angry.

I can tell several stories which outdo anything I have heard recently, and I will recount one, which seems to reveal the most serious defect with the present system. Some years ago, we published a paper in a genetics journal on a class of genetic suppressors which we argued were due to enhanced expression of an alternative gene product produced by duplications and triplications. When the genes were finally cloned we were able to get physical evidence for this hypothesis and a paper was duly submitted to a journal. It was rejected. One referee had no complaints, but the other said we should do genetic experiments to prove our point. The Editor's letter urged us to pay attention only to this referee's comments and said the manuscript was seriously defective and could not be published without the genetic experiments. The following telephone conversation then took place:

S.B.(after introducing the matter): Did you read the paper yourself?

Editor: No, I cannot be expected to read everything that crosses my desk.

S.B.: Are you aware that the referee you selected either can't read English or, more likely, is a total moron? The experiments he asks for were done and published a few years ago. They are clearly referred to in the paper, and the physical evidence supports them.

Editor: (silence).

S.B.: Who is the referee?

Editor: I can't tell you that.

S.B.: You should now accept responsibility for your bad choice and since his comment is both groundless and worthless, I assume you will now accept the paper.

Editor: No, we cannot go back on our original decision; there is no appeal.

I could cite several other instances where authors have been compelled to pay for the mistakes of editors who seem to value decisiveness more than truth and justice. It is incidents such as this that have led me to question whether the anonymity of referees needs to be guarded so closely. The standard argument for anonymity, of course, is that referees can speak their minds (if they have any) without fear of professional retribution. But it also allows their motives to remain opaque. For the innocent among you, here are two examples from S.B.'s glossary of referee's comments and their true meanings:

Referee: The treatment of the literature was cursory.

Meaning: The author has failed to quote my papers.

Referee: I am concerned about the interpretation of the experiment; the author should repeat these twenty times with different conditions of pH and temperature and wearing yellow socks.

Meaning: If I can slow him down I can get my own paper on the subject into print before him.

Removing the anonymity of referees may help, but there are more radical solutions, too. One was invented by Leslie Orgel and myself. Editors would be provided with printing inks with a range of different lifetimes from a few months to decades; they would publish everything received but would decide whether to use 2-month, 2-year or 20-year ink for each paper. At the appointed time the paper would vanish from the literature.

Another scheme suggested itself to me when I received a copy of the first issue of volume 1 of a new journal, with a title such as *The Journal of Invertebrate Psychiatry*. On the inside cover it contained the remarkable statement, "Back numbers of this journal may be obtained ...", which led me directly to the concept of negative volume numbers. Again, Editors would publish everything they received and would only have to decide when it would have been appropriate for each paper to have been published, assign it, for example, to volume –33, 1963.

In case anybody has not yet noticed, soon none of these or other ingenious schemes will be necessary because the whole system will have been 'done in' by electronic publishing. Papers are now being given publication dates when they go on the net, which can be months before the hard copy appears. The electronic pre-print with open discussion (not refereeing) will soon become commonplace; in fact, labs could go into the publication business by themselves. We will need something to substitute for the present ratings given to papers appearing in 'superior, peer-reviewed publications' (and commercial publishers will find ways of making people pay for this). Perhaps we should have a readership index; it should not be beyond the wit of man to devise a way of recording whenever a paper is read, hard-copied or cited. Perhaps papers that are not frequently consulted should be progressively consigned to slower and more remote storage facilities, and ultimately perhaps only exist as printed copies in bound volumes in one library in Antarctica.

Loose ends

Molecular biology by numbers . . . six

Sydney Brenner

Flies usually have six legs, but mutations in the *Antennapedia* locus can convert the sensory antennae into legs, so they can have as many as eight legs. For many years I tried to find out whether these were smelling legs or walking antennae, but I never succeeded in getting any reply from the professionals other than that the bristle pattern had changed and that was all that was important. In fact, one of them told me he could see a leg in one bristle, and an eye in one patch of cells. My guess is that the transformed appendage is incomplete and only looks like a leg.

Today, fly mechanics can change *Drosophila* at will by genetic tricks. All one needs is the right gene with a good promoter and wing cells can be turned into eyes. Again, I am sure that these only look like eyes and are not eyes that the fly can look with — a pity, because an extra eye on the undersurface of the wing would be useful for landing in crowded cages.

By transplanting inducing tissue at the appropriate time, experimental embryologists converted the skin of tadpoles into retina, and the eye that formed came to lie at the rear of the frog when the tadpole underwent metamorphosis. Although it would have been useful for reversing, this eye was unfortunately nonfunctional. Ganglion cells formed in the ectopic eye and axons grew forwards into the brain, interestingly confined to one column in the spinal cord. But when they reached the brain the axons ramified all over the surface, hopelessly lost.

How axons find their correct partners is one of the most fascinating problems in embryology. Years ago, I spent considerable time on this question of the accurate wiring of neuronal projections from the retina to the tectum. This retino-tectal mapping — once referred to in a journal column as the tetano-rectal projection, probably because the author had a submerged memory of the frog with the rear eye — was well restored after the optic nerve was cut in frogs, although there were some errors.

Roger Sperry formulated the chemo-affinity theory, in which he proposed that accurate wiring depended on chemical codes that brought matching neurons together. Szilard thought that would be like an antigen–antibody recognition, and because there are so many cells in the brain, and even more synapses, most neurobiologists did not think that neurons could be individually coded. In fact, one stated that there were not enough nucleotides in human DNA to code for the specificity of 10^{10} neurons in the human brain.

Such remarks are a challenge, so I invented a simple way by which something like 5×10^6 specificities could be coded for by 112 genes. It went something like this. Imagine a square array of cells and consider, for the moment, only one of the coordinates. We start at the left end, and the first cell sends a signal to its right-hand neighbour which induces that cell to turn on two genes; one of these makes a specific surface code and the other makes a signal which goes to its neighbour to induce a new state in it. We have several of these working in parallel; the first is a two-state system writing 1, 2, 1, 2, 1, 2, . . . on the array, and the second is a three-state system writing 1, 2, 3, 1, 2, 3 . . . Note that this combination defines six different cells: (1,1), (2,2), (1,3), (2,1), (1,2), (2,3) . . . All we have to do now is add more systems, each of which has a different prime number of states.

Thus, 2-, 3-, 5-, 7- and 11-state systems will give 2310 different combinations (from $2+3+5+7+11 = 28$ variables). As we need a gene for the signal and another for the code, we can do it in one dimension with 56 genes. Two dimensions need 112 genes, which would provide a total of 2310×2310, or about 5 million different combinations. These numbers increase very rapidly, so that by the time one reaches 19-state systems, one has added only another 98 genes ($13+17+19$ gene pairs) but these can encode about 10^7 specificities in one dimension and 10^{14} in two, enough for all the synapses in a brain.

Gödel, in his famous proof, used prime numbers to encode statements uniquely so that he could turn them into arithmetic; this theory used the same trick. If I recall correctly, I even provided a plausible biochemical model — a 'don't worry' theory — in which the different states were recorded as carbohydrate modifications; the decoding was done in the receptor cells by the computation of sets of enzymes that removed the modifications, and recognition was achieved only when all were removed.

My theory never saw the light of day, because although logically correct it cannot be true. Firstly, I had serious doubts about prime numbers in Nature; but more fatally, it would take too long to generate. I discovered from the biochemical literature that it took about two hours to turn on a gene and produce its protein in animal cells. The sequential process over 2310 steps would therefore take about 4600 hours to complete, which makes it impossibly slow. Also, errors in the system generate profound messes, analogous to frame-shift mutations in genes.

Paul Sigler, a crystallographer, liked this theory and urged me to publish it. I tried to think of titles: "Gödelization of the Retinal Field" was one, but the one I liked best was "Dotting the eyes".

Loose ends

Here, in Kyoto . . .

Sydney Brenner

Some of my readers may know that I have been spending a lot of my time on what I call the RIP (Research Institute Project). One day I shall have to tell the story but I think it had best be kept under wraps for some time, like British Cabinet papers. Watch this column in 2020 for revelations. In the meantime, I suppose the moratorium has expired for what I know about the founding of the European Molecular Biology Laboratory, and some of the more interesting lessons learnt should therefore be committed to paper now, before I forget them.

Setting up new institutes for research reveals many cultural dichotomies. Scientists feel that the most important thing in a research institute is research, so they want to start with real people working on real scientific problems at real benches. They want the engine first; when that is running, it can be put in the car and the road to travel will be obvious. They want to do things bottom-up.

Administrators, government officials and company executives think very differently. They want a plan. Where will the institute be sited? What directions will it work on? How many research groups will there be and how shall they be organized? And, of course, what ranks will we have, what accounting procedures will we use, and so forth. The administrators believe that once there is a plan, all that is needed is a few advertisements to find the scientists. They want to do things top-down.

All groups planning research institutes also have a scientific advisory committee to advise them on the science that might be done. Meetings always follow the same pattern. The chairman proposes that we discuss the general scientific directions. X strongly favours mouse genetics, Y argues for *Drosophila* development and Z proposes protein crystallography. This is discussed at length for several hours until Q intervenes: "This is ridiculous. How can we discuss scientific fields when we don't know who will be coming to the laboratory?".

The chairman then proposes that we talk about people and we all agree. X suggests Dr A, well known for his work in mouse genetics, Y, Dr B, who works on development of the *Drosophila* eye and Z tells us at length how terrible everybody is in the field of protein crystallography except for one person whom modesty forbids him from naming. Once more Q intervenes: "This is ridiculous. We are getting nowhere. How can we discuss people when we don't know what scientific fields we want in the institute?". The chairman therefore proposes that we move to a discussion of research directions, and so we have the classical paradox — which comes first, the scrambled egg or the minced chicken?

It is hard enough to start an institute in one country, but try starting it with several different countries. All of us do the same science but French, English and German scientists, for example, have very different views about how one goes about doing things. No German is willing to move unless the Institute has been clarified for all time in its full cosmological perspective. And no Frenchman will accept anything that has not been written down and shown to follow rationally from a few fundamental declarations. It is only the Anglo-Saxons who are prepared to have a go, to see what will happen and let it evolve without too many rules. The Theory of Natural Selection could not have been formulated in any other cultural context.

In order to probe these cultural differences I have formulated a gedanken experiment which can be transformed into a real one at any time we can get funding for the research. The leading actor is a very important scientist — perhaps a Nobel laureate — who gives a lecture to a scientific audience in different countries. In the middle of the lecture he removes his trousers and continues to the end. The question is, how does the audience respond? Here are some conjectures.

In England: it will be totally ignored. Some may privately note that it is a useful way to emphasize a point in a lecture and may put it to future use.

In France: after a short while, a man dressed in uniform will enter and ask the lecturer to leave.

In Germany: the entire audience rises and takes off their trousers (or equivalents).

In Italy: after a few seconds the lecturer realizes that his trousers have been stolen.

In America: a few minutes pass followed by the statement of the obvious "Hey man, he's taken off his pants!"

In Japan: no reaction but after the lecture someone will come up to the lecturer and say "Ah, very good. But only in Kyushu they take off trousers in that style. Here, in Kyoto, we do it this way".

The response in other countries is left to the reader.

Actually, like all good theories, this one is based on a preliminary experiment. Years ago when I visited Japan, I discovered the useful word gotcha-gotcha, which means mess, anarchy or chaos, among other things. In a lecture in Kyoto, I introduced it to describe one of my slides. The audience did not stir but at the end of the lecture, someone came up to me and said: "Ah, very good. But only in Kyushu do they say gotcha-gotcha in that way. Here, in Kyoto, we say . . ."

Loose ends

Molecular biology by numbers . . . seven

Sydney Brenner

The Cambridge group of Bragg, Perutz and Kendrew did not find the α-helix because they had been wrongly advised about the structure of the peptide bond and they were looking for helical structures with an integral number of turns. Pauling knew that the peptide bond was planar from his theory of resonance and he did not let any Platonic preconceptions guide his model building. The α-helix has a 3½-residue turn and two turns for every seven amino acid residues, which project on the same side of the helix about 10 Å apart.

Francis Crick saw that this feature would allow two α-helices to interact with each other. If amino acids with hydrophobic side chains such as leucine, methionine or isoleucine occurred every 3½ positions, with hydrophilic residues in other places, the resulting α-helix would have a hydrophobic ridge running up one side of it. Thus a protein molecule with this property would dimerize; the two helices would wind gently around each other to form what he called coiled coils and, unlike DNA, the chains would be parallel and have the same polarity.

These predictions were completely fulfilled when the sequences and structures of α-helical proteins such as myosin, tropomyosin and paramyosin came to be studied. All showed the features of the seven-fold repeat. Myosin has a strong structure repeat at 143 Å which corresponds to 98 = (7 x 7 x 2) α-helical units. When the sequences are analysed or displayed on an appropriate grid, they all show the seven-fold hydrophobic residue repeat; actually this would mean having a hydophobic residue every 3½ residues but as one cannot have half residues, between every seventh residue there is one that is either 3 or 4 positions away.

This structure motif, well known to those working with muscle proteins, reappeared much later in the guise of the so called 'leucine zipper' proteins. These are DNA-binding proteins with carboxy-terminal tails showing a clear 3½-fold leucine repeat — that is, leucine occurs at every seventh position with another leucine 3 or 4 positions away. Although a special structure was proposed for leucine zippers, there is no doubt that they are like the other cases of coiled coils and, as in the case of myosin rods, are used to dimerize the proteins that contain them. Several members of the family interact with each other, preferring to form heterodimers because they are more stable than homodimers.

We now understand clearly why so many proteins involved in gene regulation are dimers. This was first clarified for lambda repressor by Mark Ptashne. The dimer allows the same recognition unit to be used twice. Thus, if one subunit fits into one major groove, then on one side of the DNA helix, a half-turn would cover 5 base pairs. Five base pairs above this, the major groove reappears on the same side of the helix, and the same subunit would fit into a complementary sequence; the complement is required to preserve the symmetry. Then, if the affinity of one subunit for one sequence is 10^{-5}, say, the affinity of the dimer becomes 10^{-10} and specificity is enormously enhanced in a simple way. In addition, if heterodimers can form, then the versatility of DNA recognition is widened, again through simple means.

We require simple steps to achieve these changes so as to ease the evolutionary pathway to greater complexity. Why are so many proteins dimers or, indeed, higher oligomers? One reason might be molecular channelling. Thus in tryptophan synthetase which is a complex of two enzymes, A and B, there is a tunnel that allows indole, the product of the first enzyme, to reach the second enzyme, for which it is the substrate. The other is the basis for regulation of activity. The concept of allostery (which some of us thought was the way they answered the telephone at the Institut Pasteur) was that the regulating molecule had to bind at a site different from that of the substrate, because the two had different chemical structures. Often it appeared that allosteric interactions were mediated through different subunits of the same enzyme and the concept was generalized in this way. Indeed the classic case for the study of allosteric interactions is haemoglobin and here the substrate and effector are one and the same, namely, oxygen.

In the case of the feedback regulators of enzymes in bacteria, it is often the terminal product that inhibits the first enzyme of the pathway. We have to explain how this site evolved. Most probably it existed as another enzyme, and if we imagine that we continuously have mutations that change the surface properties of enzymes so they can interact with each other, productive interactions, where one produces an advantageous regulation of the other, will be retained and improved. For proteins that interact with themselves, the most probable product is an infinite helix, and this polymer may be disadvantageous. Further mutations either could eliminate the interaction or, in a few cases, could convert it so that the protein forms a dimer that then closes the polymerization.

Seven denotes perfection or completion; there are seven days in the week, seven sages, seven deadly sins. But in biology, two may be a better number for closure.

Loose ends

Francisco Crick in Paradiso

Sydney Brenner

Richard Dawkins has written another book on evolution. I haven't read it, but I noticed that one reviewer thought that the force of Dawkins' arguments was becoming diluted by a combination of militant atheism and over-flamboyant prose. To conservative scientists like me, the idea of selfish genes, while certainly snappy, leads to ignoring the biology surrounding the genes and, in the end, to a distorted view of evolution. I do sympathize with Dawkins, however: he faces a tough problem in trying to convince people that natural selection explains evolution.

The resistance does not come from any profound religious beliefs, but rather from a deep feeling that it can't work. It's very difficult for anybody to believe that making random changes in a television set, or even in the plans for a factory making television sets, will convert it from black-and-white to colour. Our common experience with anything complex is that the most likely result of tampering with it will be to break it. Human-designed systems have certain properties which stem from the nature of engineering and are related to the limitations of our mental processes. We need to impose very severe constraints on complicated designs to get anything to work. Because we are unable to talk or think about more than a very small number of processes taking place simultaneously, we isolate them into subassemblies so each can be treated separately. We also have to be absolutely explicit about how things should act in time; causality must be obeyed, and if X causes Y, then X must appear before Y. We also like hierarchical systems to make explicit the flow of control.

I used to think that these principles of modularity, rigorous sequentiality, and hierarchical control might underlie the structure and function of all elaborate systems. They are certainly true for writing a large piece of software or making a watch; in each case, even small departures from the original construction will produce a mess. I now believe that while these principles may be at the heart of artificial engineering, natural engineering is different. Biological systems have processes which are more flexibly organized and capable of displaying more resistance to lethal alterations, and have more versatility in adaptive responses.

Thus the evolution paradox resolves itself as follows. If we persist in thinking that natural systems are like artificial ones, we will need a designer to impose the same constraints on natural systems as we impose on artificial ones. And, just as for artificial systems, somebody would have to 'go back to the drawing board' to get something new. Of course, in nature, there is no going back to the drawing board: if something does not work, it is simply discarded and something new will take its place. In reality, the question needs to be turned on its head. Instead of starting with a concept of a system as we might build it, and then needing miracles to turn fish into salamanders, we should rather ask about the structure of natural (and other artificial) systems that allows them to undergo change by natural selection.

So, we need to study the 'grammar' of biological systems, and this is one reason why thinking about genes alone is not enough. We have to know the principles of construction of the system to comprehend the possibilities. This is easily seen from an example. Suppose that, upon landing on a distant planet, scientists discover two organisms; one emits yellow light, the other blue light, and there is evidence that one evolved from the other. If we were to assume that each had emission lamps, with sodium vapour in one and potassium in the other, we would require nuclear transmutation to convert one into the other. On the other hand, if we had a white light source and a prism and a slit, we could easily see how errors in the embryological development of the slit could lead to changes in the emission. In fact, all kinds of light emission become possible.

I shared an office with Francis Crick for twenty years in Cambridge. At one time he was interested in embryology and spent a lot of time thinking about imaginal discs in *Drosophila*. One day, he threw the book he was reading down onto his desk with an exasperated cry. "God knows how these imaginal discs work." In a flash I saw the whole story of Francis arriving in heaven and Peter welcoming him with "Oh Dr Crick, you must be tired after your long journey. Do sit down, have a drink and relax." "No," says Francis, "I must see this fellow, God; I have to ask him a question." After some persuasion, the angel agrees to take Francis to God. They cross the middle part of heaven, and finally right at the back, across the railway tracks, they come to a shed, with a corrugated iron roof, surrounded by junk. And in the back part, there is a little man in overalls with a large spanner in his back pocket. "God", says the angel, "This is Dr. Crick; Dr Crick, this is God". "I am so pleased to meet you", says Francis. "I must ask you this question. How do imaginal discs work?" "Well", comes the reply, "We took a little bit of this stuff and we added some things to it and…actually, we don't know, but I can tell you that we've been building flies up here for 200 million years and we have had no complaints".

This story was a particular favourite of an Italian Minister of Science.

Loose ends

The seven deadly curs'd sins ... Pride

Dear Willie,

I received your package last Monday and have spent the week reading its contents. You have no idea of how grateful I am to have something to do these days. The experiments validating your new theory of olfaction are most ingenious. Then I read the letter from the editor of *Smell* and the referees' comments enclosed. You can safely ignore the editor who has clearly not read the paper. The first referee can also be set aside as all of his comments came straight out of a word processor. However, the second referee, who seems to have angered you most, should be taken more seriously.

I know that you are proud of your work but, like most things, pride has two faces: true and false, honest and misapplied. When it is based on real quality and attainment it is a virtue, but when the self esteem is overdone it is a vice. It is not impossible that a referee has seen something you have not seen, knows something unknown to you or, by sheer chance, has found some gap in your argument. You should therefore go and do the added control, if only to prove him wrong.

I remember reviewing a paper in which the authors proudly claimed to have rescued galactokinase-negative mutant human cells with DNA from a lambda bacteriophage carrying the galactose operon of *E. coli*. The control was a normal lambda. I just did not believe the result and I suggested doing the same experiment with a nonsense mutation in the galactokinase gene. This is a text book control experiment because the two phages would differ only in one base pair. The authors' reply was that they saw no point in doing this control because it was bound not to work. Today, of course, we know that the original result is totally implausible. The authors were either misled by an artefact — perhaps carried over enzyme from the lysed bacteria — or this was a case of applying the UNF (universal normalizing factor), which is to multiply the experimental result by the ratio of the theoretical to the experimental result.

The episode I want to recount now is much more instructive. In 1960, I attended a seminar by a scientist, G (because some of the people are still alive I shall not disclose their names), who announced with great pride the result of an experiment which he believed showed that bacteriophages with every thymine in their DNA substituted by bromouracil produce no mutants at all. Since G took great delight in the demolition of standard theories of molecular biology, such as the complementary base pair mechanism of DNA replication, he was immensely pleased to show that the doctrine that base analogue incorporation in DNA causes mutation was absolutely wrong. After a few desultory questions from the audience, I got up and said "I bet you this is wrong". "How can it be wrong?", he retorted, "we have done all the controls". "Never mind", I said, "do you take the bet?". "Of course", came the reply. "The bet will be one bottle of champagne — and French, not Californian", I said, and, turning to the audience, asked "who else takes the bet?". A colleague, F, immediately sided with me, while M joined G; all the others sat gaping.

I then outlined the control experiment, which was to repeat the entire experiment, but to leave out the bromodeoxyuridine. I predicted that the same result would be obtained, even though that sounded ridiculous, and promised to explain why, if I was right, which I was. For you to understand what was going on, I have to give some details of the experiment. It involved measuring the reversion of *r*II mutants of bacteriophage T4 to r^+. The wild type grows with lysis inhibition both on the standard B strain of *E. coli*, and also on *E. coli* K12, on which *r*II mutants make no plaques at all. The *r*II phages were labelled by infecting a culture of strain B in the presence of 5-bromodeoxyuridine and growing to lysis. This phage was then mixed with some r^+ and the mixture was centrifuged to equilibrium in a CsCl density gradient. The *r*II phages banded at a greater density than the r^+ phages and indeed the difference was consistent with the complete substitution by bromouracil of the thymine in the phage DNA.

Now, I knew two things that G didn't. The first is that *E. coli* has an inducible enzyme that cleaves the bromodeoxyuridine to bromouracil, which is not assimilated. I therefore knew that the phages could not have contained any bromouracil. Secondly, a few years earlier, Sewell Champe and I had attempted to measure the size of *r*II deletions by density gradient centrifugation and to our astonishment found that they were heavier than r^+. We rapidly traced this to the fact that growth under conditions of lysis inhibition made phages lighter, regardless of genotype. By coincidence, the density difference corresponded to complete substitution of thymine by bromouracil.

I can't say I was proud of winning my bet because it was too easy and, anyway, I had private information so it was a bit unfair. But I took great pleasure in puncturing false pride. G paid the debt, but in Californian champagne. M never paid, but his sin was merely to have been seduced by what seemed to be a certainty, and perhaps he felt that enduring my many reminders of this painful debt was payment enough. As ever,

Uncle Syd

Loose ends

How do I rate?

Sydney Brenner

I have spent a lot of time writing testimonials for my students and colleagues and evaluating candidates for grants, promotion and prizes. There are some individuals I have supported at all stages of their careers, lauding them for their capacity to excel as research fellows, as assistant, associate and full professors, and even as heads of department, though the latter is quite tricky. It shouldn't be long before I start getting requests for the very last stage of all. I imagine they will start roughly as follows: "Dear Dr Brenner, Dr K has applied to be buried by our organization and has given your name as a reference. The Institute of Celestial Kinesis is interested in creative cadavers who have attained a high level of earthly accomplishment and who will continue to be creative and productive in future heavenly pursuits . . ."

In the course of my long career as a testimonial writer, I have learnt a number of important rules that should be followed. The letter must be of the correct length, not too short, which looks bad, or too long, which arouses suspicion in the reader. Just over one page is best. Much of the first page can be filled with the titles and address of the recipient: "Dr Ivor Paine, The A. Spirin Distinguished Professor of Molecular, Cellular and Developmental Neurobiology, Chairman (sorry, Chairperson), Search Committee . . . etc." The text should overflow on to the second page with a sentence such as: "Taking all factors into account, and weighing up all the pros and cons, I have come to the conclusion, that, on balance, Dr X may well have reached the demanding standards set by your Department; if not, he is certainly on the threshold and has the potential to do so in the near future."

More seriously, it is important to recount one event or a particular characteristic that singles out the individual from everybody else. This catches the attention of the reader who then remembers all the other things said about the candidate even though they are said about all candidates — they are outstanding experimentalists, have excellent backgrounds and show outstanding promise.

Another important rule is always to give your true opinion. If someone is second class, say so, even if you have to temper it by putting him in the top division of the second class. It may reflect on your ability to choose the right people, but if you say everybody is outstanding you will devalue your opinions.

All of this takes time and I often wonder whether a form letter could be composed for all occasions which only requires filling in the blanks and deleting the inapplicable. I have got as far as: "Dr . . . is in the top/bottom 100 % of all postdoctoral fellows I have known." This has the virtue of allowing the recipients to make their own decisions without being contaminated by your views. Another self-scaling sentence that could go into the form letter is: "I am certain that Dr . . . will not only contribute to, but will also gain from, the excellent scientific environment offered by your Department."

A new kind of letter is increasingly crossing my desk. This is the one requesting a performance evaluation. Common in industry, this letter has reached academe *via* administrators who have been to management schools or, at least, had a course or two. I thought I would complete one myself just to give you the flavour.

1. *For how long and in which capacities have you known the subject?* I have known him for nearly seventy years as friend, colleague and occasional confidant.

2. *How do you rate his management abilities? Comment on his teamwork and his capacity for multiplexing his activities.* He is very good in a team, especially if he is the leader and everybody does what he says. In some cases, he does let people go their own way and he will quickly adopt whatever turns out to be successful. He has always undertaken more than he can manage and multiplexes his activities only by the skin of his teeth. Over the past few years he has shown signs of forgetting what he needs to do and has been known to come to the wrong meeting on the wrong day in the wrong country.

3. *How do you rate his skills of communicating with other people?* These are excellent, except that some might say he talks too much. He is very good at persuading people to undertake projects — I hesitate to call it brainwashing — and these are frequently successful. He is a reasonably good listener, but he tends to be easily bored.

4. *What are his strengths and weaknesses that could affect his performance as a manager?* His strengths are an ability to think divergently, a sense of humour about the world and himself, and seriousness about his work. His weaknesses are procrastination and leaving everything until the last minute (and beyond), an inability to be firm with people and a tendency to spend more time inventing ingenious reasons and excuses for not doing things than getting down and doing them.

5. *Would you promote him if he worked in your institution?* If you mean increase his salary, then absolutely yes. If you mean increase his responsibility, then absolutely no.

6. *How would be you rate him on the scales provided overleaf?* AAA (superbly outstanding).

Loose ends

The seven deadly curs'd sins ... Envy

Dear Willy,

I was sad to hear that you did not get the fellowship and even sadder about hearing who did get it. You should not treat this as the end of the world; there will be other fellowships and quality, like truth, will out. Hold on to the confidence in yourself and you should know that this is shared by everybody except the members of the selection committee. It is occasions like this that arouse feelings of envy in those who have failed but, I can assure you, there is no need for this in your case. Envy is the worst of all sins because almost nothing good can be said about it; it involves, by its very nature, malice and ill-will directed at those who have succeeded, and discontent in those who feel slighted and overlooked.

Yet when you come to think about it, it is completely paradoxical. Envy has associated with it the feeling that those who have attained the desirable are undeserving, or at least, less deserving than oneself. In that case, the standards associated with success are clearly deemed to be inadequate, so why should one want to have succeeded anyway? This is a variant of the Marxist (Groucho) paradox, which, you remember, occurs when one declines membership of a club on the grounds that it has stooped so low as to invite people like oneself to join it. In our case, however, we have to ask why anyone should wish to join a club that has refused entry to people like oneself. In fact, there are clubs that have members superior to oneself and, in this case, envy at not belonging is clearly neutral.

I am extremely envious of Darwin, but it is impossible to begrudge him his success and demand that he should have waited a century or so to allow me a fair chance to compete with him. Likewise, I envy Andrew Wiles who proved Fermat's last theorem, but it would be ridiculous for me to ask for additional time to learn enough mathematics to offer him competition. Wanting the desirable but unattainable is very different from failing to get the desirable and potentially attainable.

As you go through life you will find some things that are undesirable and (only too easily) attainable which will come your way. Here is a partial list: acting as a committee chairman, becoming the head of a university department, writing reviews, editing journals, organizing meetings and, worst of all, attending these meetings and finding yourself confronted with a transcript which has to be translated from a Ukrainian dialect into a form of English.

Those who know how to escape from these undesirable activities are worthy objects of envy for they have learnt to conquer other sins, such as senses of duty and service, responsibility to the community, and so on. Envy of such people is almost good; malice is certainly not involved and one wishes only to emulate their success. Sometimes this form of enthusiastic envy can inspire novelty, invention and ingenuity in the great mission of rendering the undesirable totally unattainable. It is sympathy for one who had not succeeded in this mission that led me once to write to a hapless friend along these lines: "Dear Joe, I wish to offer you my sincere condolences on your appointment as Director of the Any Institute. It is at times like this that ones thoughts are drawn to many lamented and departed friends."

You will need to have an armoury of devices to help you to avoid these terrible events. In my time I have deployed many, all unpatented and most kept as closely held trade secrets. In avoiding the undesirable one should not be offensive but rather ensure that the end result is favourable to everybody and especially to oneself. Take the following situation which will happen over and over again in your life. You are invited to give a lecture and you agree to do so on the telephone as part of a pleasant conversation. After accepting, you will receive a long letter telling you about the department, who you are going to meet, etc., and asking for your CV, a short twenty page biography, and a thirty page summary of your main scientific achievements. You are asked to fill out a large number of forms wanted by the University, the State and the Federal Government, all wanting a piece of your $100 honorarium. There may well also be permits for human experimentation, fetal research and genetic engineering, but I have never got to the bottom of the pile.

Finally, there is a request for a recent photograph. I used to respond by saying no photographs of Dr Brenner exist but people thought I was joking. There were those who proved me wrong by asking for the original of a blurred picture discovered in a country newspaper in Japan. I then modified my approach by sending a slightly pompous letter saying that I had asked my photographic department to deal with this. After a few days a letter was sent enclosing a picture of a pink beribboned white kitten. Within three days another letter was sent apologizing for the frightful error and enclosing a picture of a ferocious looking dog. Usually this made the point and I have never had to use the crocodile, but I dreaded the day when I would meet my match in somebody who, in a brilliant counter-move, would publish one or perhaps both pictures.

I have just looked up envy in the dictionary and found it has two meanings. One has the some derivation as invidious — ill-will. Another comes from the Latin, *invitare*, meaning to challenge, or vie. Perhaps this envy is a virtue. Warmest regards,

Uncle Syd


Loose ends
by Sydney Brenner
1997

Loose ends

Pathogenetic tales

Sydney Brenner

A little over twenty years ago, a group of scientists assembled in Asilomar, California, to consider the consequences of the newly invented techniques of genetic engineering, or recombinant DNA, as it later came to be called. There was in place a moratorium recommended by scientists and which we, working for the UK's Medical Research Council, had been instructed to heed by the Secretary of the organization. It was then that I came to appreciate the depth of the distinction between chastity and impotence, which I had used some years previously to convince my supervisor, Sir Cyril Hinshelwood, that bacteriophage resistance arose by mutation in *E. coli*, a process he seriously doubted at the time. The outcome is the same, but the reasons are profoundly different.

Fortunately, at Asilomar, scientists voted to terminate the moratorium, and, in exchange, offered to proceed cautiously and try to find conditions for the safe practice of gene manipulation. This occupied the attention of many able scientists for several years thereafter. If nothing were to survive from that decade other than the proceedings of committee meetings, the reports of commissions of enquiries, press reports and books, future historians would convince themselves that a new religious cult suddenly appeared first in California, later sweeping the world with intricate theological works that encompassed not only everything on earth but future human evolution as well.

Eventually a scheme was produced in the US, the NIH guidelines, parts of which were plainly absurd. For example, the guidelines required that the pathogenicity of the organism providing the DNA be taken into account; thus DNA from the malaria plasmodium required higher containment for cloning than DNA from *Tetrahymena*. Nobody was allowed to consider how the original pathogenicity might be reconstituted from a bunch of DNA clones, and, if one took this seriously, lion DNA would need more stringent containment than pussycat DNA, lions being much more pathogenic for humans than their domestic cousins. It took quite a long time to convince people that the best way to deal with a dangerous virus would be to clone it and lock it up in *E. coli* or lambda bacteriophage rather than working with the virus itself.

All of this generated a discussion of what could be called artificial pathogenesis. Could we create, intentionally or by accident, entirely new elements that were worse than anything found in nature? I wrote a paper on this subject (which was published by Her Majesty's Stationery Office as an appendix to the Annual Report of a Committee) in which I tried to invent novel pathogens which could be realistically produced.

My favourite example was to clone the gene for ricin (a toxin famous at that time; see paper in *Bulgarian J Murd. & Assass.*) in lambda bacteriophage and propagate it as a lysogen in *E. coli*. Many years later, it turned out that I was not all that original, when it was discovered that a toxin from *Shigella* (a close relative of *E. coli*) was a homologue of ricin, and what is more, the gene was carried in a lambdoid bacteriophage. This serves to illustrate that the limits of pathogenesis are not set by putting genes together; novel gene encounters will happen, albeit rarely, even across species. What is more important is how well these agents do in the outside world. The problem is not about genes but about the environment. Man has created more good and also wreaked more havoc by environmental intervention than by tinkering with genes in a laboratory.

Today we have another good example of a novel pathogen that was not created by scientists, but is of natural origin and which has produced a new disease entirely through social means. Bovine spongiform encephalopathy (BSE) has reached us because we have eaten cows that have eaten other cows that ate sheep, in which the disease is endemic. Most scientists considered prions, the protein infectious elements that cause scrapie and BSE, to be improbable; many thought that even though radiation inactivation of scrapie seemingly excluded the presence of nucleic acid, some would eventually be found lurking in a hidden recess in the protein complex. In fact, as long ago as 1967, John Griffiths recognized that it was theoretically possible for a protein to generate more of itself by turning on a gene that produced it. Modern theories of prions have the bad protein converting a good normal protein into the bad state by some structural means.

Because prions can be transmitted by eating them, human prion diseases would become epidemic if cannabilism was widely practised. To prevent BSE in cows, all we have had to do is stop involuntary cannibalism amongst herbivores, despite the considerable economic and social consequences.

Not only are scientists blameless for creating the 'new' prion diseases, they probably couldn't have done so if they had tried, especially without knowing of the existence of prions in nature. I therefore urge that we enjoy our impotence by calling for a moratorium on research leading to the creation of prions.

Loose ends

The seven deadly curs'd sins ... Sloth

Dear Willie,

You are not unique; I hear many complaints these days about the laziness of graduate students and post docs, and how spoilt everybody has become. I have friends who can remember blowing their own glass, building amplifiers with valves, purifying enzymes and synthesizing substrates. It seems that nobody can do anything without a kit today, and I suspect that many experiments are left undone simply because a kit is not available. In this new era of kitsch biology, experiments that require a respectable amount of preparatory work will not be done and many laboratories that have invested in a field and accumulated a stockpile of clones, antibodies, etc., will guard this store carefully. Or at least they will until the field becomes exhausted or boring, when the reagents will become part of the catalogue of a Kitco. One day a commercial genius will discover a way of providing the results as well as the means of doing the experiment, and perhaps, in conjunction with an enterprising journal, will also see to the publication of the results.

Everybody who talks about the past begins with the words "In my day", and I shall be no different. In my day, the normal working week was about 100 hours, 14 hours a day for seven days. General improvements in working conditions did not seem to affect scientists. I realized what a good deal our employers were getting when I received a letter some years ago officially informing me that the working week had been reduced to 37 hours. In my day (there it is again), we divided scientists into owls and larks. Owls turned up at the laboratory after lunch (or just before if it was to be a good one) and worked through the night to 4 a.m.; larks came to the lab about 4 a.m. and stayed until 7 p.m. There was a hybrid species that came to the lab about 6 a.m. and stayed until 6 p.m. and then returned at 8 or 9 p.m. for the midnight session. I was a hybrid for many years but have become more of a lark in the past fifteen years.

As you can imagine, the ideal partnership was that of an owl and lark. They could keep experiments going continuously and still have enough time together to discuss what should be done next. Discussion took place in the afternoon as the early morning shift change was too brief and, anyway, both partners were semicomatose at that time.

What did we do at the lab? When I started experimental research, I was taught quantitative physiological chemistry, as it was then called. I assayed glucose, urea, amino acids, sodium and enzymes in a variety of bodily fluids and tissues. We had to work hard because a large number of measurements were required to achieve significance and reproducibility. We also learnt all the statistical techniques that go with this work, and before we could begin to study the effects of one or other hormone on blood iodine levels we had to prove that our measurement techniques were reliable and that repeated assays on the same material gave the same results. It was here that I learnt to deal with intrusions of the entropic universe by doing experiments wearing yellow socks and facing east. This rigorous approach did not apply to large areas of descriptive biology, such as neuroanatomy. After all, determining where the cerebellum is does not require several independent descriptions, followed by taking the mean and the variance. However, the quantitative urge could not be quenched and I spent many hours counting neuron cell bodies in sections with a *camera lucida*.

Genetics was different, and when I became a 'phage geneticist and learnt how to do it in binary by looking for yes or no answers in spot tests, I found a new road to biological problems that did not require statistical tests of significance. Someone once asked me how we knew our results were significant. I replied that we plotted the results on 7-cycle semilog graph paper and if we could see a difference from the other end of the room, they were significant.

Phage experiments were not only easy to do but they could be done quickly and simply as spot tests, as Seymour Benzer first showed us. Why then did we work round the clock? The answer is that we spent many hours sitting in a coffee room talking. A visitor to the lab, ignorant of what we were doing, would have found it a den of apparent sloth; for much of the time, most of the people seemed to be engaged in talking in a room littered with dirty coffee cups and overflowing ashtrays. We were not evading work but simply finding ways of avoiding unnecessary work by carefully working out the simplest, most elegant and most revealing experiment. Once found, a quick visit to the laboratory sufficed to do the experiment, then back to the coffee room for several hours until we could look at the results and proceed to another bout of discussion. Calculated sloth, in this way, produced the best answers. By proceeding more slowly (whence sloth) and not lurching into any old experiment just because it could be done, we actually made more rapid progress.

All of this was quite hard to explain to people on the outside, especially those who thought that science was done according to some scheme of hypothesis, deduction and experiment. Science is more human than that and even the most discouraging human faults can be turned to good purpose. Next time you pass the coffee room, you can be assured that everything is well if it is full of students talking and arguing about their work. As ever,

Uncle Syd

Loose ends

In theory

Sydney Brenner

Molecular biology has been a great leveller and has made thinking unnecessary in many areas of modern biology. With the disappearance of theory has also come the decline of experimentation, and the practice of science by hypothesis and testing is not known by many students in the field. So powerful are contemporary tools for extracting answers from nature that pausing to think about the results, or asking how one might find out how cells really work, is likely to be seen as a source of irritating delay to the managerial classes, and could even endanger the career of the questioner.

There was a time when we lacked this direct contact with the molecular level of living organisms and had to probe it by indirect means. We had no other alternative but to have ideas on what might be there and then design experiments to test the ideas. This was the period when the term model was very much in vogue; there were models of gene regulation, protein synthesis, recombination, chromosome replication and many others. The main arguments between authors and referees were whether the experimental results offered supported the model uniquely, or whether alternative explanations were possible. Scientific meetings were more interesting because real argument was possible and suggestions for new experiments could be discussed.

The truth of a theory had two aspects: the first was whether it was correct, that is it contained no logical inconsistencies; the second, and more important, was whether it corresponded to the situation in the real world. I recall a meeting in the 1970s where a speaker presented two different models of transposition, which we can call A and B. The climax of the talk came when the speaker triumphantly declared that there were only two possibilities: "Either A is right and B is wrong, or B is right and A is wrong." He had to be reminded that he had overlooked a third possibility which was that they were both wrong.

These and other experiences led me to suspect models or theories that had been built when only some of the facts where known. So for dealing with models of how neurons might interact to produce behaviour, I invented a sceptic who would always ask: "How do you know there is not another wire that comes up the back of the animal and does something you have not accounted for?" Unlike in physics, where we might be able to deal with the 'another wire' sceptic on general principles, the only way to do so in biology is to be able to say that we know all the wires and therefore that there are no other wires. I use 'wire' in a general sense: good theories of molecular or cellular networks will need knowledge of all the connections.

Many of our discussions resorted to the use of Occam's razor. This allowed one to formulate the simplest hypothesis by cutting away extraneous hypotheses. Of course, quite often neither the simplest theory, nor the most elegant (another popular word of the time), turned out to be right. We knew so few facts that quite frequently a hypothesis had to be stretched out to encompass them all. I found that many people were applying, what I called Occam's Broom, which was used to sweep under the carpet any unpalatable facts that did not support the hypothesis.

For a time, I thought that having a model with one's name attached might be the path to immortality in science. It seemed even better than having a conjecture in mathematics because the 'Brenner Conjecture', which sounds wonderful, could always be disproved and replaced by the 'Dampener Theorem'. (Mathematicians tell me that lemmas are very chic and much safer than conjectures.)

In experimental science, it might appear that a piece of equipment is the thing to have: there is the Pasteur pipette, the Büchner funnel, the Petri dish, the Erlenmeyer flask, and so on. However, these are all becoming obsolete and the robots that are replacing them are called after the companies that make them. My plan of acquiring fame second-hand by taking an additional surname to become Bunsen-Brenner would have come to nought, except possibly in the third world.

I need to confess that I have always wanted to be a theoretician but until computers were invented I could not deal with mathematics. I spent hours of my youth trying to understand embryology or, as we call it today, developmental biology. I read Needham, Waddington and even Woodger. At one time I even understood the different meanings of induction and evocation.

This nonsense prepared me for attending a select and secret conclave of biologists who met in Woods Hole in the 1960s to discuss such matters as whether differentiation was a 'state' or a process, and what was the difference between these anyway. I was able to say it was both and to illuminate the difference by pointing out that 'mellowing out' was a process whereby one attained the 'laid back' state.

Actually, the orgy of fact extraction in which everybody is currently engaged has, like most consumer economies, accumulated a vast debt. This is a debt of theory and some of us are soon going to have an exciting time paying it back — with interest, I hope.

Loose ends

The seven deadly curs'd sins ... Intemperance

Dear Willie,

Thank you for the case of wine which was delivered today; what a splendid birthday present! You certainly know my weakness and I hope that there will always be a Beaune of contention between us. I often think I should have taken up the molecular biology of the grape rather than messing about with worms and fish. There could have been an *Institut de Oenologie Moleculaire* and we might even have seen some biotechnology companies with names like Chateautech, Vintage Genes and Sham Pain Pharmaceuticals. I have noticed that some of the best genomes for study come from things that are good to eat; perhaps there is still time to found Gourmet Genetics Inc. with oyster and lobster genome programmes.

We are being pressed today not to indulge in excesses and to do everything in moderation. It seems that we have all inherited large numbers of terrible genes from our parents and that all the pleasures of life are very bad for us. Have you noticed how every new discovery of a bad gene is announced with screaming headlines and how the scientists involved behave with cautious delight in television interviews? I wake up every morning in fear that I will be told that I have a gene that makes me sensitive to the traces of hafnium in Pinot Noir grapes.

The current trend to give genes a bad name distracts people from the fact that a lot of their genes are pretty good. Some years ago I found that every family has its Uncle Frank. He is the one who smoked 60 cigarettes and drank two bottles of vodka every day of his life from the age of four, had six wives and innumerable girlfriends, and raced Ferrari cars. Unfortunately he was killed in a mountaineering accident at the age of 92 in the Himalayas. I have tried, in vain, to interest scientists and politicians in starting the Uncle Frank Genome Project so we can get hold of all these good genes. I have been told that the Uncle Franks of this world are only lucky; but I don't accept that as a satisfactory answer. The genetics of luck seems like a good subject to me, and much better than the genetics of alcoholism or homosexuality.

Actually, the association of intemperance with alcoholism is relatively recent and its extension to sodium, cholesterol, animal fat and tobacco is very modern. In general, intemperance means the pursuit of any passion to excess. Science, as a passion, cannot easily be practised in moderation and, anyway, who is going to judge what is excessive. You will remember that Mendel was accused of fiddling his results because it could be shown that the precise numbers he reported were very unlikely. I'm certain that he did not invent the numbers, but he certainly knew when to stop counting. I can see him saying to himself that there is no point in carrying these experiments to excess, that one has to stop somewhere and that now seems as good a place as any. Perhaps if he had continued he would have noticed something interesting about the numbers and would have become the father of statistics and forgotten about genetics.

It is statistics that tells us whether we have done enough. Most molecular biologists know nothing about statistics and care even less. I was awoken from my slumbers at a lecture the other day by hearing the words Student's *t* test, which most people in the audience thought had something to do with sampling the refreshments in the college canteen. The speaker needed this test because he was studying molecules using the electron microscope that he could hardly see — the molecules, not the microscope — and he needed something objective to tell him that he had distinguished his faint objects from the noisy background. My molecular biologist colleagues, however, felt that if this was what it took to get a result, the speaker would be strongly advised to drop his line of research for one where a clone is a clone and a gel is a gel.

I am almost ashamed to confess that I have been learning statistics again. The first time I did so was 40 years ago, when my teacher was someone who was trapped in Denmark during the war and spent four years in an internment camp spinning a coin and using the results for an experimental introduction to probability theory. Curiously enough, his strings of H's and T's remind me of the gene sequences that I am studying now. I have collected enormous numbers of sequences, found some very interesting things, but don't know where to stop. Every time I think this must surely be the end, I reach for the computer and find some new little twist, and occasionally something important. I have learnt to be very wary of running the standard programs, which I think conceal important features so that I can't see the wood for the phylogenetic trees. We seem, somehow, to have got the wrong combination in joining artificial intelligence with human stupidity. I would like to see more people doing it the other way round.

Well dear boy, here I sit, a glass of Pommard in one hand, intemperately tapping the keys of my computer with the other. I have promised myself this will be the very last sequence and I will then sit down and write my paper. As ever,

Uncle Syd

Loose ends

A retiring fellow

Sydney Brenner

A short while ago I received a letter asking me to step down from membership of a board on which I had been serving for quite some time. Normally I refuse to join boards or committees unless a finite, and preferably short, term of service is fixed in advance. But this particular job was not very onerous, I enjoyed doing it, and worst of all, I thought I was doing some good.

So when I read the letter, which, I should say, I had been expecting for several years, I was surprised to hear this little complaining voice within me.

"They're getting rid of you", said junge ego.

"True, and about time", replied alte ego.

"But", shrieked junge ego, "who can possibly fill your place?".

"It doesn't matter", replied alte ego, "anybody will do, and you and I can certainly use the time".

"Perhaps you should appeal . . .".

"No, let's write the letter and go and look for another job".

I have already retired from three jobs and much more gratefully from all the committees and advisory boards that accompany a successful scientific career. Mandatory retirement from boards is a wonderful idea, but for those who wish to remain actively engaged in science, retirement is a source of worry, and increasingly so as that sunset date draws closer.

In Japan, where the age of retirement is 60 in some universities, its advent is especially feared, and several of my friends have actually become ill as a result of their retirement. One day you are right at the top, the next day you are thrown on the rubbish heap, and perhaps even forbidden to visit the department. No wonder gastric ulcers are a common disease amongst retired biology professors in Japan. In other countries, you may be offered a small office where you can get your papers in order and write your memoirs, or at least leave something decently organized for your obituarist. I have known departments where so many of the offices were occupied by past distinguished members that there was almost no room for anybody else.

Mandatory retirement was made illegal some years ago in America, but I am told that there are numerous loop holes and administrative tricks used to circumvent the rules. They can make continuation dependent on outside research funding, which transfers the decision to a group of individuals who are not sympathetic to either the very old or the very young.

One story told to me, which I was assured was absolutely true, concerned the retirement of a professor at one of the more 'serious' universities. Apparently, everything had been done to ease his departure. There was a one-day symposium with talks by the more prominent of his past students, and a retirement dinner with speeches and a presentation of a parting gift. At the end of all this, he rose to reply, and calmly informed all gathered there, that he had just discovered he did not have to retire, and that, in fact, he was considering legal action. He assured his audience that he was not leaving and that they should dry their tears, as they would be able to enjoy his company for many years to come.

I thought at the time of hearing this story of transforming it into an apocryphal tale, adding an ending in which, on his way home, the man is waylaid in an alley and beaten up by a gang of masked assistant professors, who confirm his retirement by unconventional means. The gang members, of course, have been awaiting the professor's retirement so that they could be candidates for his tenured professorship.

Administrators will tell you that mandatory retirement is necessary so that they can promote younger people, and so enable everybody to move up the ladder. But that is the way administrators think and, anyway, the issues involved are really about the control of resources, and not about research. We all know scientists for whom retirement at the age of 35 would not be considered too premature, and conversely there are others, with more decrepit bodies perhaps, who could still outshine the best post-doc you ever saw. I am glad to say that there are 35-year-old scientists who realise that research is not for them and go off and join the biotechnology industry or become editors of scientific journals. And the ancient combatants will always find a way to do research if that is what they want to do. After all, they know all the ropes.

In all my retirements, I have so far been able to avoid attending the celebrations of the final symposium and the farewell dinner where I would be presented with some absolutely useless gift to be used in my retirement. I have seen them all — sets of garden tools, golf clubs, elaborate cooling equipment and so on. There is this myth that scientists are longing for the day of their retirement and can't wait to start indulging in all of the hobbies and activities that they had to set aside while they had their boring jobs of research. This, as every committed scientist knows, is utter rubbish.

I hope that the editor will allow me to use this column to let anybody who may be planning a party for me know that I would very much like a multiprocessor work station and an electron microscope as parting gifts. And now, if you will excuse me, I have to go and look for another job.

Loose ends

The seven deadly curs'd sins . . . Avarice

Dear Willie,

You must have surely seen that our good friend Dr C. Quince, has been given yet another huge grant from The Thanatology Foundation for a large project to find human genes for avarice and venality. The factories keep on multiplying and growing and I hope you are never tempted to acquire a dark, satanic mill of your own and join the band of new alchemists who turn gold into base pairs.

Some historian of science will observe that during the 20th century, scientific research became industrialized, first in physics and then in biology. We changed from cottage weaving to textile manufacture. Some scientists discovered that owning the means of production was better than owning the product, because they got everything that way. You will remember that this is what Karl Marx was not happy about in society and his recommendation was that this ownership be taken away from the small minority and given to the proletariat —something, I think, that may not be too far from the thoughts of our present scientific working class.

Perhaps we would be better off modelling ourselves on feudal Japan, where the peasants always owned the land but the lords owned the produce and therefore needed a samurai class to defend their acquisitions from other predatory lords and to indulge in predations of their own. Of course, to achieve a balanced ecological system, they had to ensure that they did not kill too many peasants or destroy too much land in the course of their activities. Could research fit this mould? It is easy to see the lords walking off with the produce, taking all the results and publishing them, because this is what they do today. But it is harder to find a plausible basis for the ownership by students and postdocs of all the labs, chemicals, clones, computers, etc. And who would be the samurai, helping one lord to take over another department?

The industrialization of scientific research has gone hand in hand with the transfer of the science to industry. Until the late 1970s everybody thought that molecular biology was not only useless but dangerous, but with the development of the biotechnology industry following advances in DNA cloning and sequencing, everything changed. There appeared on the scene venture capitalists, who set up companies to pursue the commercialization of the new biology. For the first time, scientists encountered avarice in its purest form.

I was once told by a venture capitalist that he assumed great risks, that nine out of ten of his companies failed and that he had to work very hard to ensure the single success. I therefore proposed that he should set up a company for me, which we could call ToLose LowTech Inc. I would volunteer to be one of his failures, so that after giving me the money, he need not waste any more of his valuable executive time on me. In fact, I would be happy to have all nine of the failures so to allow him to focus all of his energies on the one success. Noting once that for every project aimed at turning biomass into energy there was another trying to turn energy into biomass, I also proposed that they were paired on the same industrial park and connected to each other with appropriate pipes and valves, with the flow simply regulated according to the prices of raw materials and oil. Perhaps the saving grace of the biotechnology industry is that some of the scientists who become businessmen were better at business than at science. Of the businessmen who have attempted to run the science of a company, I don't know of a single success.

Once I was asked by a television interviewer to appear on his programme to discuss why I went into science. "The answer is easy," I said, "it was not for the money or for the glory, it was for the girls." He asked whether I would say this on the air and when I said I would, he rapidly disinvited me. Actually, I went into science because I was greedy. When I was young and the world was still a place of innocence, I wanted to be a scientist because I had an insatiable hunger for knowledge. Not for me the fox, who knows a little about many things, nor the hedgehog, who knows a lot about one thing; I wanted to be something like an octopus, with tentacles everywhere, and know everything about everything. I soon discovered that the knowledge discovered in books could be exhausted and so to satisfy my greed I turned to research to find new knowledge of my own.

On reflection, I see I have not distinguished carefully enough between hunger and greed. Hunger seems to be more virtuous because it involves an end that is elusive and unattainable; the hungry man is never satisfied because he never finds enough to eat. The greedy man, on the other hand, usually finds food easily but goes on eating even when sated. There is also the difference that the hungry man has less than he justly deserves, whereas the greedy man has more.

I feel quite hungry now, and need to go to the lab to find something to eat. Yours

Uncle Syd

Loose ends

Centaur biology

Sydney Brenner

I have been reading John Horgan's entertaining book *The End of Science*. Entertaining, because the book is based on interviews with scientists and philosophers, many of whom are familiar figures and all of whom emerge as large as, if not larger than, life. The thesis is that the physicists' dream of a Final Theory of Everything — The Answer to all Riddles — will soon be realized, whereupon everybody will be able to down their scientific tools and take up embroidery or Thai cooking or surfing or any other activity they have foregone for working in the lab. If we take some of the direr prognosticaters seriously, it is likely that even Thai cooking will have come to an end and there will be nothing left for humanity to do.

More than thirty years ago, Gunther Stent predicted the end of molecular biology and he later generalized this not only to the end of biology and all science but also to the end of art, literature, progress, everything. His argument was that the exponential growth of science and other human endeavours could not be sustained forever and would come to an end when all resources had been consumed. For science, this means that all problems will have been solved, and we will know and understand everything. The universe, it seems, would have come in with a big bang but it would go out with a little whimper.

Gunther Stent's precise example was that once we knew both the structure of DNA and that nucleotide sequences encoded amino acid sequences of proteins, and that once the principle of gene regulation had been found by Jacob and Monod, there was nothing left to do. Thus embryology could be accounted for by simply turning on the right genes in the right place at the right time and that was the solution to the problems of development. Not only did we not have to bother investigating the developmental biology of the millions of different species of animals and plants, but there would be no motivation for scientists to pursue those fields because the mystery had vanished. Like many others since him, he thought that scientific attention would move to the new frontier of the nervous system.

Somewhere I read that in mathematics and science many problems are not solved but simply vanish as people learn to ask different questions. Indeed, if we look back at the questions being asked fifty years ago in biology, we find it difficult to understand why biologists thought them significant at the time. In much the same way, the 'answers' that are provided each day in biology prove to be inadequate quite a short time later as our view of the subject deepens. DNA replication has been 'solved' almost annually for the past forty years.

Biology differs from physics in that organisms have risen by natural selection and not as the solutions to mathematical equations. Many years ago, I heard the great theoretical physicist, Eugene Wigner, give a talk on the non-physical or 'miraculous' properties of biological system. He contended that it was not possible to derive a sufficient number of equations to define the quantum states and that something else had to be involved — possibly consciousness.

I pointed out that if I took Professor Wigner and decomposed him into an ensemble of elementary particles, the chances of these reassembling into the same Professor Wigner, complete with accent, were zero and would indeed require a miracle. But Professor Wigner and other biological organisms are not made by condensation in a bag of elementary particles, but by some very special processes that are, of course, consistent with the laws of physics but could not easily be directly derived from them.

The trouble with physics is that its deepest pronouncements are totally incomprehensible to almost everybody except the deepest physicists, and while the pronouncements may well be absolutely true, they are all pretty useless if my aim is to understand *Escherichia coli*.

In biology it is the detail that counts, and it counts because that is what natural selection had to accomplish for there to be anything at all. We want to know which genes are turned out and exactly where and precisely when. To view natural selection as a kind of handwaving process that seeks refuge in glorious generalities when it cannot solve problems, is the anthropomorphic reflection of our own insufficiencies.

I have heard it said that adumbrating the end of science in public is dangerous because it might lead to the drying up of research funds and to turning off the interest of young people in science. But biology is open-ended and will remain so, and when we have finished with fish, ants and human beings we can profitably start with centaurs and other mythical beasts. The Greeks produced centaurs by artistic transplantation surgery; the torso of a man was glued to the end of a decapitated horse. What better way of spending a few years than asking whether a centaur, with its six limbs, two thoraces, two alimentary tracts, and other complications could be constructed by a developmental program encoded in genes? And if so, could we actually make one?

Loose ends

The seven deadly curs'd sins . . . Ire

Dear Willie,

After your call I thought I should write to try to persuade you not to take any of the drastic steps you were contemplating yesterday. Anger has only scalar properties; it has magnitude but no particular direction. I know you are furious about having your papers turned down, but threatening the editor with public horse-whipping or sending him a letter bomb, although clearly attractive, are a bit ludicrous, and unlikely to give you any real satisfaction.

I am not saying that you should swallow your anger and forget about the episode completely. What you will find is that the wheel of fortune can often turn uncannily in your favour, and wrath contained and remembered can often yield pleasant revenge. I am now going to tell you a story you must promise not to repeat to anybody at all, which is why this letter has "Burn, then read" written on it, although I assume you ignored that. It concerns the editor of an important biological journal who had submitted work for a PhD in biochemistry. I had been appointed the external examiner. We read the submitted material, and then there was an oral examination during which I asked a few eccentric questions. I then retired to a room, and drafted a report along the following lines:

"This thesis deals with the subject of gene expression and especially with the expression of genes in mammalian cells. Parts of it are very speculative and not supported by any direct experimental evidence. These sections could form the contents of another thesis for submission to a different faculty in the university, perhaps Moral Sciences or Divinity. The remainder of the work is quasi-repetitive, repeating on humans experiments that have already been extensively carried out on tardigrades and kangaroos. This might well be submitted for a PhD in biochemistry at the University of Bishop's Stortford, where it will find the audience it so richly deserves. I am unable to recommend the award of the degree as it is not up to our standard, but I hope that the candidate can be encouraged to submit again when his work has reached a more definitive stage."

He got his PhD because I threw the draft away and instead produced a standard report. This was not because I knew that the internal examiner, who behaved in a polite — some might say fawning — way, would have refused to accept the draft version. Instead it had dawned on me that I had no objective grounds for exacting the vengeance I had planned, because I had never had a paper rejected by that particular editor. Nor would it have been right for me to act as the agent for the host of unknown authors who had received rejection letters from him, as I was then the editor of another journal and had honed the skill of writing such letters to a fine art. But most importantly, if the editor's PhD had been denied, and had he then discovered that it was on account of what I had written, if he had any sense, he would have waited for the wheel of fate to turn again, as it must do by reason of symmetry. I saw myself as an aged man, living in poverty, and begging him for some part-time work, such as reading proofs or even making the office tea, while he enjoyed the pleasure of a terrible vengeance.

Nothing I have said applies to anger directed against inanimate objects, and particularly against experiments that do not work. I strongly support the right of everybody to shake incubators with rage, to kick centrifuges with fury, and to smash test tubes that absolutely refuse to give the right answer. I am told that expressing your anger in this way is much better that swearing at your technicians or going home and beating up your wife and children. However, I think such action goes beyond pure personal therapy; it is very important to discipline all those recalcitrant pieces of lab junk to bring them into line and show them that you are not one to submit easily to defeat, especially if it is their fault.

I can hear you dismissing psychokinesis as claptrap, but I have some astonishing experimental results to support it. The late George Streisinger and I one night decided to test the psychokinetic effect. We took two sets of Petri dishes, A and B, and I asked George to put stack A on the left and B on the right in the incubator before we went home. At home, we were to concentrate our thoughts on stack A and instruct it to "Grow, grow", and then focus our minds on stack B, telling it: "Don't grow, don't grow." Next day we found that the only difference between the stacks was a slight positive bias towards growth in the B stack. In discussing what had gone wrong, I discovered that George had mistakenly put stack A on the right and B on the left in the incubator and it immediately became clear that the experiment was a great success. Because of the switch of plates, we had largely neutralised one another's powers, with the small positive bias in stack B being the result of my stronger psychokinetic force, possibly because I lived closer to the lab than George.

We tried to get this experiment published but failed because the referees kept on asking for controls. They could never see that this was one of those rare experiments that is its own control. Yours,

Uncle Syd

Loose ends

How the quest was won

Sydney Brenner

Not long after Jim Watson's *The Double Helix* appeared, there was talk about making a movie about the DNA story. The author of the book took this very seriously and did not find all the many suggestions made to him very helpful. One idea put forward was that Jim should be played by Woody Allen and Francis Crick by Peter O'Toole. Another was to do it as a musical with a dance based on the entwining DNA chains. Eventually, it was the BBC that made a film, in which the part of Jim was played by Jeff (*The Fly*) Goldblum, who later went on to greater scientific fame in the film of *Jurassic Park*.

From the very beginning, I came to the conclusion that the real question about transferring *The Double Helix* to the silver screen was what kind of a story it is. Is it a comedy? Or is it a romance, or an epic or an adventure story? The BBC's portrayal carried some of the saccharine romance associated with tales of Oxbridge — there were echoes of *Brideshead Revisited* — but there was also a strong dose of the 1950s and something reminiscent of the novels of Kingsley Amis (remember *Lucky Jim* — a title actually suggested for the book).

I talked to some of the potential producers of the movie. One I remember well because I discovered he had written all of the scripts for the Dr Kildare movies and had worked with Lionel Barrymore. He felt that one of the difficulties about making the film is that there is no action in the story and, for the most part, nothing happens to keep the audience interested. There are just a lot of people sitting around and talking all day or scribbling on pieces of paper. Put that way, it sounded to me more like an Antonioni film.

Actually, when I spoke to this producer, I was so dazzled by his credentials that I forgot to tell him that I had solved the problem many years ago, and that I even had a sketch of the script which I could make available for the right price. As with all my other suggestions, I could not persuade Jim to take my script seriously. As the years pass, it has become increasingly unlikely that it will ever be made because I required everybody to play themselves and many of the actors are no longer with us.

It is set as a Western of the classical form. The location is Fudge City, a typical dusty one street town, at the end of the railroad and at the gateway to the Far West. All the characters are looking for the DNA lode, and, in particular, for a map showing how to find it. The map was either lost a long time ago or, more likely, had never been drawn. I can only give you brief sketches of the characters and a glimpse of some of the scenes.

The mayor of Fudge City is Larry Bragg, dressed in typical formal Western style with striped pants and a top hat, and played by Sir Lawrence Bragg. Rosalind Franklin is the school marm, Linus Pauling owns a large ranch, called the Lazy A, and a mine. On Saturday nights, the boys ride into town and may be found cavorting in the Crazy Helix Saloon. Many lose all of their wages playing cards with Francis Crick, in the full dress of a Mississippi river boat gambler. On some evenings the boys amuse themselves with a half mad prospector, played by Erwin Chargaff, who has hitched his four mules, Adenine, Guanine, Cytosine, and Thymine, to the rail outside. Maurice Wilkins is the English railroad owner who occupies a private rail car, decorated in resplendent Western Victorian style. (Don't forget the large enamel bath.)

The arrival of the greenhorn from back East is a scene to relish. Jim Watson has been sent West by a group of Eastern bankers who would love to lay their hands on the DNA lode. On a hot day the train pulls into the station. Out steps Jim in a black suit with trouser bottoms well above his booted ankles. His scrawny neck is encircled by a collar several sizes too large, and a black hat, several sizes too small, shields his slightly bulging eyes from the glaring sun. He clutches a cardboard suitcase with his meagre possessions. There is no one to meet him.

The story moves on to the meeting in which Francis teaches Jim a new card game called Model Poker. Then Pauling claims he has found the map, but Jim and Francis know it is wrong because the water is in the wrong place. They produce their own map. There is much rejoicing, including a tremendous party in the saloon that allows many other people to play small parts.

We move to the final scene. In the telegraph office at the railroad station, Max Perutz, played by himself, with a green eyeshade shielding his puzzled eyes and with his sleeves held in place by elastic armbands, sits tapping out the news of the find. The camera closes up to the tapping key and fades in scenes of telegraph lines going to every town. The DNA lode has been found! There are shots of newspaper headlines announcing this and we fade to a series of frantic scenes of people fighting for seats on the trains, of buying supplies, loading wagons and whipping horses, as, in every quarter of the land, the Great DNA Rush gets underway.

I even sketched a sequel, to be called The Return of the Screw. There was a wonderful scene of a high noon shoot out between Marshal Nirenberg, played by Marshall Nirenberg, and an elegant Mexican gunman dressed in black (*pace* Cat Ballou) played by Severo Ochoa. The rest, as they say, is left to the reader's imagination.

Loose ends

The seven deadly curs'd sins . . . Lust

Dear Willie,

In today's climate of political correctness, I shall have to be very careful in choosing my words in this letter, because I do not want to stand trial for conspiring to provoke lewd behaviour, should our private correspondence fall into the wrong hands. The modern meaning of lust has very bad connotations. It suggests uncontrolled sexual desire or an overwhelming craving for money, fame or power, all of which are related to sex, anyway. And it implies that the people who lust for all the lustable things don't merely desire them but also go out and acquire them, often by unpleasant means. Perhaps this is a post-modern meaning, because those who only want such lustable things will probably be unsuccessful in getting them, either lacking or suppressing the fearful beast of action within themselves.

I have found that there is a whole body of biological theory dealing with this subject that has, to my knowledge, never been put together in one place. (It also occurs to me that the subject itself would make an admirable four-letter journal title — LUST, a journal devoted to research on the baser aspects of biology.) The general theory, in brief, states that all the bad and sinful things within us are legacy from our animal past: they are a relic, if you like, of earlier evolutionary stages. In later stages, when we became human beings, these were no longer absolutely essential for our survival, and so mechanisms evolved to contain them. This took place at the time our brains underwent dramatic changes and we discovered that smooth talking could succeed where brute force would not. Although it is unclear what changes took place in the genome to turn crocodiles into venture capitalists, we are pretty sure how this is represented in the phenotype. It resides in the brain, and clearly the animal in us lives in the older mid-brain while the human part is probably in the cerebral cortex and particularly in the enlarged forebrain.

The contemporary preoccupation of neuroscientists with problems such as vision, memory, language, consciousness and thought has led to a neglect of the more interesting part of our brains that directly controls our basic physiology and baser psychology. My guess is that the key to this will be found in the hypothalamus, and we should all be hard at work on this part of the brain rather than studying long-term potentiation of synaptic function in the hippocampus or having arguments about neural Darwinism. Research on the hypothalamus should also be much more financially rewarding than work on any other part of the brain, because this is — or if it isn't, it ought to be — of great interest to pharmaceutical companies. One example should suffice to convince you. When you are ill with what is called 'flu, you feel absolutely terrible. Quite often you will run a temperature, you will certainly feel depressed, and you will lose sexual desire and your appetite for food. All of these symptoms suggest that the hypothalamus is involved and we know that most, if not all, of them are the unwanted side-effects of the elevated levels of α-interferon that accompany 'flu.

Unfortunately, we don't yet know enough about the pathways and receptors that mediate these affects of interferon to modulate them with drugs. For example, a severe bout of 'flu may be the best way to lose a lot of weight rapidly, even if it cannot be recommended (just as we are unable to endorse surgical decapitation as a cure for headaches), but if we knew how to stimulate that pathway, lots of pounds (of both kinds) could be made to move. Again, if we could find a drug that quenches the awful malaise and depression of 'flu without counteracting all the good things happening to our defenses against the infection we would have something of great benefit to humanity. One could feel absolutely wonderful while lying ill in bed. Actually I have to tell you that, based on personal experience, there is already one such drug on the market. It's called Single Malt Scotch Whisky. I think that the cheaper and more generic varieties of blended whiskys will also work but this is based on far fewer clinical trials. I have no information at all on the efficacy of Bourbon whiskey.

Unfortunately, the entire theory of lust is probably wrong mainly because the notion of the partition of our brains into the animal and human, or the instinctive and the rational, not only runs through all of psychoanalysis but has also been endorsed by many religions, although not many got as far as talking about brains.

You should know that lust was originally a word with neutral connotations, simply meaning pleasure, and related in origin to the word list, meaning to wish or to be inclined. In this sense, I could say that I lust after truth in my scientific work or that I have a lust for knowledge. These are virtues much to be desired, and it was only when theologians and others got hold of these words and made them sins, that they came to be used as terms of reproach and were given the mark of the beast and condemned to our mid-brains.

I feel the 'flu coming on again and need to take some medicine. Yours,

Uncle Syd

Loose ends

Bacteriophage tales

Sydney Brenner

A correspondent has asked me about the origins of a legend which has become known as 'The phage in the letter'. Common to all variants of this story is the following: one scientist, called X, sends a request to another, Z, for a particular bacteriophage strain which Z has discovered. Z replies saying he is not sending it out. X thereupon plates out the letter and retrieves the phage from it. Some versions include a third scientist, Y, to whom the outraged X takes the letter; it is Y who advises X on how to recover the bacteriophage.

Now Z, in this story, is Norton Zinder, who discovered an RNA phage, f2, in the sewers of New York and who did not send out the phage to the large number of scientists who requested it. He also found a single-stranded DNA filamentous phage, f1, in the same sewage. Both f1 and f2 would only grow on bacteria with a sex factor. It has been suggested that I was either X or Y in the legend; that is, I either plated out the letter myself or got somebody else to do it. In fact, this is an invented story and, with one exception to be recounted later, I do not know that it has ever been attempted.

I can now disclose the origins of this legend, which has a rather complicated prehistory. Readers of this column may have noticed that my generation spent a lot of time devising ingenious solutions to various problems which could have been handled more promptly and more simply. Among these was the perennial problem of what to do with the person who first sends you a request for ten phage strains, which you send by return, and then immediately asks for another fifty cultures, whereupon you begin to regret that you had answered so promptly. It never occurred to us that we could simply refuse at this point with the cry, 'Enough is enough'. No, the response had to be complicated and mysterious.

The bane of every bacteriophage worker's life in those days was bacteriophage T1. This phage resists drying and once it gets into a laboratory it is almost impossible to eliminate. Raging epidemic infections of bacteriophage T1 have been known to wipe out a laboratory in a matter of hours. George Streisinger and I invented the idea of a phage in a letter as a deterrent to those who kept on asking for strains. All requests would be met, but the letters would be liberally sprinkled with bacteriophage T1. When the recipients contacted us again with more requests we would send them some word of sympathy about the terrible disaster in their laboratory and apologise for not being able to meet any further requests as we had given instructions that all their correspondence was to be incinerated on receipt, for fear of passing on the infection.

When Norton Zinder published his paper on the RNA phage, I thought of writing to ask him for a sample of it (or f1, for that matter) because I wanted to use it to test bacteria for the presence of sex factor. However, I knew that if I gave this reason he would not believe me, and would suspect that I had made it up, simply to get the phage and work on RNA replication. Many people complained to me, and I am sure to others, about his not turning over his discovery to the world instantly, and there was much talk about how everything should be made available once it is published. I did suggest to more than one of these people that they should try to recover the phage by plating out the letter. Perhaps I was guilty of hinting that I had successfully done this myself.

I obtained many of these phages myself simply by going to the Cambridge sewage plant and bringing back a bottle of their best vintage and plating it on bacteria with a sex factor. Prodigious as New York sewage might be, we could still match it. Other people also went to their particular sewers and found their own phages, some of which, such as Qß, an RNA phage, and M13, a DNA phage, became more famous than the original finds. I didn't want to add to the confusion, but to this day still use my isolates to test bacteria for their sex.

François Jacob told me that whenever he wanted a phage he would take himself off to the nearest *pharmacie*, where all kinds of phage were sold as remedies for intestinal complaints. I traced the history of these and found that many had been isolated from the Paris sewers by two characters called Sertic and Boulgakov. The X in phage QX174 is not the letter 'eks' but the Roman numeral ten, indicating that it was the 174th isolate from a particularly good sewer in the *Xe arrondissement*.

The nearest I came to surreptitiously obtaining a microbial strain was when David Secher was working in Cambridge on a monoclonal antibody to interferon. After David had managed to get Charles Weissmann to send a bottle of extract containing the valuable cloned interferon, I urged him to plate out the contents to see if we could recover the strain that had produced the interferon. Charles phoned anxiously a few days later because he could not remember whether he had filtered the extract before sending it to us. David could reassure him that, having followed my instructions, he could confirm that the extract was sterile. Of course, Charles is of the right vintage to know that he could have added some T1 to the extract to make doubly sure that we did not acquire his interferon clone!

Loose ends

Academic dynamics

Sydney Brenner

There have been attempts to reform universities and other centres of higher learning but a correct solution to the difficult problems posed by these institutions has yet to be found. It now appears clear that until we have a rigorous theory to underpin this field, all changes will be empirical, haphazard and unlikely to produce the desired effects.

Our small group has been quietly investigating this field over the past few years with the aim of establishing Academic Dynamics as a scientific discipline, to be incorporated into the world of learning and research. Although some progress has been made, the group has unfortunately been steadily reduced in number by the erosion of biological time and it has become increasingly urgent to document some of its more important findings before it vanishes completely. We had originally planned to have our own journal, *MAD* (*Memoranda on Academic Dynamics*), but this has not been possible. I am delighted therefore that the editor has allowed us to publish some of our work in this journal. Selection has been difficult, but here are three excerpts that I hope will stimulate further work.

Collision theory

You have doubtless all heard it asked: What shall we do if Professor X gets run over by a bus? Sometimes this is said to convey the sentiment that Professor X's continued existence is absolutely essential to the survival of the institution, but quite often there is the underlying hope that such an event would be a happy one, opening up new possibilities for changes. Now, assume that the institution has a Department of Academic Dynamics (established at the same time as the Department of Bank Robbery, which solved all of the institution's financial problems) and that among its many items of major capital equipment there is a bus, suitably disguised as a number 71. The simple task of eliminating Professor X would then be assigned to first year graduate students.

The Pharaoh configuration

This is a scheme which offers a solution to the fundamental problem of all scientific departments, which is how to get rid of the old — both people and science — and create space and resources for the young and the new. Our elegant answer is to treat all scientists as Pharaohs; thus, when a senior scientist retires, he and all of his research associates, post-docs, students and technicians are sacrificed and buried in a specially constructed pyramid, together with all of their equipment to enable them to continue research in the after Life Sciences. At one blow, space would have been created for a new professor and a new group, without any arguments and with none of the rancour that usually accompanies such events.

It is obvious that this needs to be carried out only once. Thereafter, all that would be required at the appropriate time is for two men to arrive, equipped with surveying equipment and tape measures. A new pyramid would be laid out in plain sight of the present occupants, who would instantly vacate the premises.

There is a conjecture that not even one pyramid need be built; a rumour could be propagated that one was built in a little visited place such as Rangoon or Blackpool or the Bronx. This myth could be reinforced by postcards, entries into guidebooks and eyewitness accounts by reliable collaborators.

Reversed flow kinetics

We show here how, by the change of only one parameter, nearly all the problems can be directly solved. This idea was originally conceived in the 1960s when students were angrily demanding a role in university government. Some also wanted to decide on what research should be conducted, as well as what should be taught. This was the period when some Departments of Sociology thought of teaching courses in urban rioting. And it became clear that the root cause of the conflict was the desire of students, mostly male, to kill their fathers — Oedipus wrecks, so to speak.

This insight lead directly to a remarkably simple solution, which is to reverse the flow of males through the university, while keeping that of females the same. Thus, at the top of the university there would be several thousand 18-year-old male vice-chancellors with a few mature women who would be able to control them easily. At the other end, a few elderly men who had spent a lifetime studying carotenoid biosynthesis, *hox* genes or laser physics would now be first year undergraduates studying French Literature or Confucian Philosophy along with many young women who would benefit greatly from the company of the mature men. Of course, there would be a broad zone, covering 25 years, that would encompass both males and females doing graduate studies, post-doctoral work and, indeed, most of the productive activity of science. Thereafter, the sexes would part, the woman ascending into higher administration, the men descending into higher education.

Any university vice-chancellor or president wishing to pursue these matters further should know that much of the technology is covered by issued patents, but licences are freely granted for a small consideration.


Loose ends
by Sydney Brenner
1998

False starts

Titles

Sydney Brenner

This is not about knights and dames, nor is it about jazz musicians, such as Duke Ellington or Court Basie. Rather, it is about a most important issue in science, which is the difficult task of choosing titles for seminars, lectures, scientific papers, books and even the titles of the journals themselves. Today, we all have to compete for readers and listeners, and in the current ruthlessly competitive market conditions, a boring title will not be much help.

Once upon a time, everything was simpler. Journals had straightforward names like the *Journal of Physiology* or the *Biochemical Journal*. Notice that these journals are British: their founders saw no need to add a national descriptor, having got in first. There are similar journals in other countries; in the USA, for example, we have the *American Journal of Human Genetics*. An interesting question is whether "*American*" journals were named out of national pride, or to get the journals to the top of any alphabetical listings, where they would be more visible. Not quite to the top, of course, but there could hardly be much competition from Albania, which is not renowned for its scientific research. In Germany, many of the early journals were called after their founders, who personally owned the journal: Hoppe-Seyler, Roux, Virchow and Liebig had their Zeitschrifts, Arkivs and Annalen. Those were also the days when one wrote papers with straightforward titles, often numbered (in Latin, of course) in series; so we published *Biochemical Detoxification CCLXII* and *Chymotrypsin Inhibitors DCIX*.

All of this changed quite suddenly in the early sixties. A new style of writing emerged, which I will call the Massachusetts Declarative because it began in Cambridge, Mass. Its origin, I believe, can be traced to Jim Watson's book *The Molecular Biology of the Gene*. No longer did one write "Experimental evidence for the role of the ribosome in protein synthesis", but rather "The ribosome is the seat of protein synthesis". The cringing style of writing that gave us "The evidence of the present findings does not lend support to the conclusion of Spiegelberg *et al.* that DNA is replicated in the Golgi apparatus" has gone; today, we can say "Spiegelberg *et al.* are wrong". I find that being able to refer to myself as "I" rather than as "the present author" is a welcome liberation (and I can't understand people who prefer to follow the Queen and call themselves "we"), even if the rather heavy multiple authorship of most papers precludes its common use.

The same movement produced better titles for journals. Ben Lewin started *Cell* — 100 years ago it would have been called *Benjamin Lewin's Zeitschrift für Zell Biologie* — and with it a new style of publishing papers. One can think of other snappy four letter word titles for journals in fields such as reproductive biology or excretory physiology and *Junk* would be a good title for a new journal of genomics.

Incidentally, I note that *Cell* has budded again to produce another offspring with the cumbersome title of *Molecular Cell*. I am sorry that the Editor did not take my advice at the original fission event to call the daughters *Hard Cell* and *Soft Cell*. The former would be the ideal vehicle for molecular biology while subjects like immunology and neurobiology could go into the latter and move up as they improved.

Most papers still have straightforward titles but there is a tendency for them to be quite long. Perhaps these are designed to impart most of the information of the paper to the busy readers who do not even have enough time to read the abstract. Jokey titles may be found in abundance in the sections of journals devoted to news and views, mini-reviews and other items for one to peruse. The names of *Drosophila* genes (but not those in *C. elegans* where we cleverly forestalled the joke merchants by calling nearly all the mutants *unc*) and the abbreviations of signal transduction components lend themselves to titular abuses such as "A scute as achaete" and "X-static regulation". I once suggested to my colleagues in the chromatin field that the subunit should be called a karyon, preparing the way for a commentary entitled "Eukaryon screwing".

There is now considerable striving for jocularity in seminar titles, so much so that the subject matter is often quite mysterious. I invented a title that could be used in different permutations on many different occasions. The canonical form was: "Simple Thoughts on Complex Genomes" but one could also have "Complex Thoughts on Simple Genomes" and two other variants as well.

I tend to delay sending a title for as long as possible and once, when pressed for titles of my general lectures on a visit to India, I thought of offering two: one in the field of astronomy called "The Black Hole of Calcutta" and another in the field of Literature called "Lady Chatterjee's Lover". In the end, my courage failed me and I sent a boring title like "Genetic Analysis of Complex Systems I and II".

Titles are an area neglected by those who study the history and sociology of science and I hope that my remarks will stimulate the growth of an important new research field. Unfortunately, I can't yet think of a title for it.

False starts

Other sciences … the stars look down

Sydney Brenner

Although most of the journals professing to cover all sciences concentrate their attention on biology, a few still have a fair number of papers in other sciences. Most of the readers of this column probably don't have time to look at these, but I read them, and especially the ones I don't understand too well, in the hope that their very strangeness might shake up my mind to think of something new.

In particular I am fascinated by astronomy and have been since the time an astrophysicist told me that he had been to a meeting to discuss what had happened in the first 10^{-30} seconds of the Universe. Not knowing too much about the field. I told him that I knew the answer: if one had listened carefully, one would have heard: "Oh, damn!" These days one does astronomy to see if light can be thrown on cosmological theories, and the field is replete with amazing objects, such as black holes, invisible matter and naked singularities, the last being a great name for a cabaret group.

I might as well give the dire news at once. It appears that all is not well in astronomy because it seems likely that the Universe is younger than the oldest stars. Shall I repeat that? Some stars are thought to be older than the age of the Universe, an impossibility that tells us that one, or both, of these assertions cannot be true. Readers who are interested should consult the excellent general paper entitled 'The Age of the Universe' in the *Proceedings of the National Academy of Sciences* 1997, **94**:6579–6584. I first encountered this problem in a paper in *Scientific American* in November 1992 and have felt uneasy ever since. I am amazed that referees and editors allow people to publish papers with such blatant contradictions but, as we shall see, it seems that the weightier the problem in this field, the more light-heartedly cavalier its treatment.

First, I need to sketch some of the technical background. Everything depends on the value of the Hubble constant, which describes the expansion rate of the Universe and is given by the recession rate of a galaxy divided by its distance. The former is measured by the red shift of the spectral lines. The latter can be obtained by measurements of the luminosity of variable stars called Cepheid variables. The trouble is that two values of the Hubble constant have been obtained, one of 50 kilometres per second for every megaparsec, or 5×10^{-11} per year, whereas the other is twice as much, 100 km/s/Mpc, or 10^{-10} per year.

The age of the oldest stars has been determined independently from luminosity measurements of what are believed to be old stars in old clusters. The best fit implies that the age of these clusters is 16 billion years, which gives us a minimum age for the Universe. This is consistent with the lower estimate of the Hubble constant, which puts the age at 15–20 billion years, but not with the higher one, which astronomers prefer and which places the age at about 11 billion years.

Critical people, like ourselves, will want to know quite a bit more about the measurements themselves, such as their reliability; and as there are some heavy theoretical engines behind all of the arguments, we would also want to know more about the underlying models. (But we can't ask whether we would get the same result were the whole experiment repeated.) The initial measurements, it turns out, may have been flawed, as the telescopes were earthbound and affected by the Earth's atmosphere, and the detectors were not very good. Even with better detectors and the Hubble space telescope, the Hubble constant, at 80±17 km/s/Mpc, is still rather high.

It is when we come to the theory that we find there is room for all sorts of fixes. Determining the age of the Universe (t_0) from the Hubble constant (H_0) depends on making assumptions about the composition of the Universe. It was predicted that $H_0t_0 = {}^2/_3$, on the assumption that the Universe is composed of 'normal' matter and that it is flat. But for the measured Hubble constant and the age of the oldest stars, $H_0t_0 = 1.28$, about twice the expected value. It is possible that this discrepancy is the signature of 'missing physics' in the big bang theory. Einstein proposed adding a cosmological constant to fix the mathematics of the theory of general relativity. He thought the Universe was static, so the term was added to stop it expanding. When Hubble showed that the Universe was expanding, Einstein abandoned the cosmological constant. Now many cosmologists want to put it back. It is associated today with the energy density of the vacuum and it would require some new physics to make it interesting. For example, a mere 10^{-120} correction to quantum gravity would do the trick, something that appears to me should not be beyond the reach of a clever theoretician. Or, one could question whether the Universe is flat. Apparently, there is no evidence for its flatness, only theoretical prejudice. Or again, there could be missing matter in a new form.

After reading all of the fine print, I came away relieved. It was not so bad after all. The theoreticians could always fix things for us, probably because they had fixed things the wrong way the first time. I also came away with hope, because many of the issues can be settled by observation and by making more and better measurements. That, after all, is what Galileo taught us.

False starts

Net prophets

Sydney Brenner

Statements that "we have come to do biology in a new way" or "there is a new paradigm in biological research" are now commonplace. Nobody seems to be satisfied by a single good experiment that gives a precise answer to a well formulated question, which was the old way we did biology. On the contrary there is now a belief that a mass attack on parallel fronts can provide a database of all the information in one concerted effort, and all we need is a computer programme that will give everybody all the knowledge they need.

Much of this stems from genome projects, especially the effort to sequence the human genome. However, there are subtle differences between the different cultures that have generated the sequences. The yeast genome was sequenced by a co-operative venture of many small individual scientific groups, who had a deep interest in the result. Surrounding the project was an even larger group of yeast geneticists and molecular biologists who knew how to use the sequence in their experimental work. The sequence was the path to the genes of yeast; there are now ways to access all of the genes directly and the page in the Book of Life devoted to yeast is written in real DNA. The sequence has become the tool for research that it was expected to be, and not a end in itself.

It is likely that the genome projects for *Caenorhabditis elegans* and *Drosophila* will have the same impact on their fields, mainly because of the large number of researchers who can immediately make use of the product. It is with the vertebrate genomes that we find a new idea coming to the fore. Roughly speaking, the proponents have come to believe that computers can extract biological significance directly from DNA sequences.

This approach has generated two new areas of activity. One, Bioinformatics, is simply pretentious; the other, Functional Genomics, is ridiculous. The latter uses the former to try to find function from the sequences of genes. I don't think that there are any university departments devoted to these subjects but there are certainly a growing number of companies doing one or both. Other areas are now adopting the same approach of systematically assembling data by factory methods. The proteome is emerging from two-dimensional electrophoresis of proteins, but is still a poor relation of the genome. I expect to see the glycome and the lipome next.

Actually, there is already a perfectly good name for the science of studying gene function; it used to be called Genetics. Geneticists have always been interested in function and have always used their research as a way — perhaps the way — to analyse complex functions of organisms. The sequences of genes and, better still, the pieces of DNA that correspond to the genes, replace what could only be achieved by the mutant hunt in classical experimental genetics; they are tools and not ends in themselves. We will still need to find out how each gene works and piece together the elaborate network of gene interactions by the old paradigm of experiment. In fact, sequences also offer us the possibility of interpreting Nature's experiments in evolution, but that will come later as a consequence of knowing the genetics of contemporary organisms.

Bioinformatics has its place. Its main activity has been beneficial in that masses of data can now be easily reached and used for research. However, the idea that sequence data can have other information added to them which will give us knowledge of function is surely misplaced. For this, we must do more than repackage what is known; the computers must compute, and in order to do this we need a theory that we can test. The subject that will be developed will be one that should be called Theoretical Biology, but as this has a bad name we call it Computational Biology.

The siliconization of biology has been successful — perhaps too successful — in one area, which is in the way we communicate. I note that many researchers are now spending several hours a day with their e-mail, reading and sending messages to an increasing number of correspondents. I fear that this is going to put everybody in an electronic committee in permanent session. I have installed a very narrow pore filter on my e-mail; I have someone else read it and print out what I need to know. I started this mainly because a dentist in Philadelphia sent me voluminous messages about his new theories on the brain, and also because I cannot remember my password.

More than ten years ago, when electronic mail was still a novelty, I was given an account on a private network. Three passwords were requested to enter the system, and had to be renewed at frequent intervals for reasons of security. I used all twenty amino acids and the five nucleotide bases, and I then started on them again but written backwards, which makes a surprising list from which I particularly liked enilav, but there is also a enicuelosi, which has a good Italian ring to it. At the risk of compromising my computer security I shall disclose my favourite password which is ELCID, usually with some number attached because greedy computers want six characters. This password lets me login to the computer but apparently another one is needed for e-mail, which is a secret even from me. I am also toying with the idea of having a special address for bioinformaticists and functional geneticists to reach me. How about unclesyd@gnome.zurich.pri ?

False starts

Hidden agenders

Sydney Brenner

As many people more important than myself have come to realize, sexual harassment is taken very seriously, particularly in the new world. Although it is not yet in the class of murder, arson and bank robbery, it is now a common lace-collar crime and quite easy to commit, even by accident. I know this because I once attended a meeting by mistake and listened for a few minutes to a talk on sexual harassment in the veterinary industry of southern California, before I realized that the speaker was not going to discuss the folding problem.

My first encounter with sexual harassment was in a notice sent to me by the administrator of a research institute. I immediately replied asking where and how I could apply for it as I had not had any for some time. There followed a visit from the lady concerned, who sternly lectured me on the subject and who would not accept my excuse that I was a PI (politically incorrect, not principal investigator). Since then I have been extremely careful, especially in walking down corridors in the laboratory, making sure that my unsteady progress can not be interpreted as making "blocking or impeding movements", a hallmark of the offence.

Imagine my surprise, then, when I received an invitation to a party a few weeks ago with the words "Girlfriend … is something bugging you?", emblazoned in large black letters over a pale leaf-green background. An organization called Women Incorporated was exhorting me to attend a do — in sneakers or stilettos — and to join San Diego's most successful women business owners in a warm, friendly, fun atmosphere. I was told I would find no big egos, stuffy attitudes or hidden agendas, which I assumed was a veiled reference to the absence of men from this organization.

At first I thought that this was a joke played on me by one of my friends but a brief investigation showed that the organisation and the card were authentic. I checked that the card was actually addressed to me, which indeed it was, and that gave the game away. Like Leslie, my first name can be attached to either sex, and there are probably few self-respecting male Sydneys in southern California.

Did I go to the party and, more importantly, what did I wear? I confess that I was strongly tempted to put on my stilettos and a sequined ballroom gown *à la* Danny la Rue. However, as about one hundred women were expected to attend the party, my appearance there could have been horribly misinterpreted and I might even have had a class action brought against me. So, reluctantly, I decided not to go, even though I have entertained a secret desire for elaborate cross dressing ever since, many years ago, my trousers were accidentally dissolved in concentrated NaOH in the laboratory on a Saturday afternoon. Of necessity, I made a skirt out of a large paper bag (used for disposing of petri dishes) and was walking — hobbling is perhaps a better description — home, when I heard a motor car pull up behind me. The two policemen who jumped from the car and picked me up must have been disappointed when, in response to their considerate questions about my condition, I asked them whether they knew anything about ion-exchange chromatography as this was crucial for my explanation.

I have now decided to put the ambiguities of my name to good use and to start Aunt Sydney's agony column to deal with all the difficult problems encountered in laboratory life. I urge my readers to write to me but, in the mean time, by sheer coincidence, my first letter arrived today.

Dear Aunt Sydney

I am a graduate student in the department of Molecular Biology at the University of (name withheld). I am 6'4" tall, weigh 220 lbs, of a pleasant disposition and thought good looking by my friends, who particularly admire my black beard. My outside interest is tree-felling. My research supervisor (the head of the group), is a real terror and is making my life a misery. She is 4'6", weighs 100 lbs and does not have a black beard. She is said to beat graduate students, but in all fairness I have not seen or experienced anything like this. But she singled me out the other day and was really quite nasty using words such as "dumb oaf" and "stupid hulk". It is true that I mixed up two gels and forgot to do the control experiment, and I did leave the centrifuge running all night, but I didn't let all the mice escape. What shall I do? I have reached the end of my tether and plan to give up molecular biology for Elizabethan poetry.

Yours, S.G.

Dear S.G.

If you can prove that you are being treated this way because you are a male and not because you are a graduate student, you could bring an action for sexual harassment. I fear this may be difficult, however, and as you will know, society and the law offer no protection to graduate students. The best thing to do is get your PhD as quickly as possible. Enquire whether your university has a Remedial Science department to help you in the laboratory. I strongly advise you not to go anywhere near an English department as conditions there are much, much worse.

Yours, Aunt Sydney

False starts

Of human bandage

Sydney Brenner

I was the worst medical student in the world. I was reminded of this a few weeks ago, when, on a plane from Osaka to London, I was asked to look at a passenger who had collapsed and was lying unconscious in the rear cabin. Having issued the required warning that I was not a real doctor, that my knowledge of medicine was rusty and my knowledge of medical practice non-existent, I agreed to help because there wasn't another doctor on the plane.

I found the man sprawled across two seats, out to the world. His pulse was strong and regular, so no coronary. I tried to find out if he was a diabetic but nobody knew him. When I smelled his breath, it was very beery. I noticed that he was very warmly dressed, prepared for the English winter with a heavy tweed suit, a thick sweater and, peeping out from the bottom of his trousers, long woolly underwear. I advised the crew to put him somewhere cool and let him sleep it off.

When I returned to my seat, I began to worry. What if he was a case of Kreutzer–Sonata syndrome and that, even now, he was slowly turning green and his fingers were falling off, one by one? Perhaps I should have found a penknife and with the help of the attractive blonde attendant, performed a craniotomy — or was it a craniectomy? Later, when I was told by the attendants that my patient had recovered completely, I was most relieved that my original diagnosis of over-indulgence had been correct. Even later, it occurred to me that he might have been a very clever malingerer who had feigned the attack to acquire a first-class seat and escape from some boring companions.

I need to explain now how I became a medical student. I entered medical studies in the University of Witwatersrand in Johannesburg, South Africa, in 1942, because that was the only subject close to science for which bursaries were available. When, at the end of the second year, it was discovered that I would be too young to qualify as a doctor at the end of the course, I diverted to a medical science degree in anatomy and physiology. Then I stayed on for a further two years doing research in cytology and cytogenetics while, on the side, actively pursing my interests in palaeontology and archaeology.

In 1947, I was strongly advised to complete my medical degree, as positions for people with my kind of interests only existed in medical schools, where I would be considered a second-class citizen without a medical qualification. So I went back for four years.

I did not like clinical medicine. In fact, I was thrown out of surgery ward rounds, when a pompous statement that "surgery is an exact science like chemistry or physics" by a perfectly spherical thoracic surgeon induced in me an outburst of hysterical laughter. Nor was I popular with the surgeon who was repairing severed wrist tendons when I pointed out that he was joining them up the wrong way, especially when a sterile anatomy text book showed that I was right. I spent most of my time doing research in the laboratory and some of my best juvenilia was done while I was moonlighting from hospital rounds.

When I was forced to do a subject, I was able to do well in it. I got a first class in obstetrics and gynaecology, because I had to go into residence and there was nothing else I could do for three weeks. I also got a first class in forensic medicine because the professor thought I had a poor attitude to the subject. He cancelled my examination, at which I had performed badly, and made me come in every day to perform post-mortems. I was able to help my friends to pass their examinations by performing some of the more critical moves for them and, when I finally took my examination, the professor, who had assiduously coached me for the past week, congratulated me on my performance and gave me a first class. All I did was obey orders.

I squeaked a pass in surgery but failed in medicine. My theoretical knowledge was very good, and I got through one of my cases by asking the subject "What do they say you have?" It was the second case that sank me. This was a diabetic patient, and I am told that what annoyed the examiner most was when I responded to his question of what I could smell on her breath with the answer "Maclean's toothpaste." This was absolutely true, and it masked the smell of acetone, which is what he wanted me to smell. Six months later, at second go, I passed, after receiving some instruction in the subject from one of my friends.

Although I resented it at the time, I later came to realise that I had attained a wide knowledge of biology of the most interesting organism of all, ourselves. I had done anatomy in detail, I knew a lot of physiology and I had mastered embryology, even to knowing the formations of the greater and lesser omentum. Unlike the many of my contemporaries who had come to molecular biology from physics, I had come in the other direction, from physick. And today, when I see that many young doctors are mastering molecular biology, and that clinical research has accepted the molecular approach, I realise that perhaps medicine was, and still is, the best way to enter the subject.

Oh, by the way, I forgot to say that when I smelled the breath of the comatose patient, I was pretty sure that it was Kirin Ichiban.

Magazine

False starts

Inventing science
Sydney Brenner

When I was young, we seemed to have plenty of free time available for activities that the more serious generation of today would regard as puerile, if not infantile.

Thus I spent endless hours writing scripts for imaginary series such as the 'Lives of Great Composers' or 'Great Moments in Science'. I remember a scene written for one of the former which depicted Berlioz in a morgue, fondling the hand of a departed lady (as he once really did, by the way), and singing to himself, "Your tiny hand is frozen. Ah! I must tell this to my friend Puccini."

One of my Great Moments in Science was to enact the 'rediscovery' of Mendel's laws in 1900 by Correns, Tschermak and de Vries. The setting is a pub, in which the three inebriated principals are simultaneously trying to explain to each other, in heavy German accents, the 3:1 segregation of tall and dwarf plants. In true Stanislavsky style, the performers have themselves indulged heavily before the play and give performances that somehow also include the cell theory and the structure of chromosomes.

I also spent months writing a whole book and giving lectures on 'The Chemistry of the Neuranes and Their Derivatives'. These included the neurotic acids, which could not decide whether they were liquids, gases or solids, and schizophrenic anhydride — a remarkable compound with a negative time of reaction. And so on.

With this valuable training, it was quite easy for me to meet the challenge posed by a friend, Sidney Bernhard, in the late 1950s, that we should write a paper that was clearly nonsense but which could conceivably fool an editor who was not really knowledgeable into accepting it. At that time there had appeared one of the first journals to make rapid communication its speciality and the editor we had singled out as our target was Jacques Monod. Because Sidney, who was a very talented pianist, and I, with a number of different voices, became more interested in performing 'Excerpts from the Great Operas', the paper was never submitted, but the text survives. Here it is. Alas, the figures and tables that accompanied the manuscript have been lost, but, as they say, their reconstruction is left to the imagination of the reader.

Neutron transferase, a new enzyme found in the bacterium *Prevaricator transmutans*

Sydney Brenner and Sidney Bernhard

We wish to report the identification of an unprecedented enzymatic reaction, found in extracts from a bacterium enriched from soil collected near to the nuclear reactor at the Atomic Energy ----------, in ---------- (name and address removed by the censor).

We noticed that cultures of this bacterium become radioactive if they are grown near a neutron source. The particles emitted are ß⁻ particles with an energy of about 1.5 Mev and arise from a radionucleide with a half-life of about two weeks. A remarkable property of the cultures is their ability to grow after a long lag period in medium that totally lacks a source of sulphur. Even more astonishing is the fact that when methionine is isolated from bacteria grown under these conditions, the sulphur is found to be exclusively S^{32} and none of the other naturally occurring stable isotopic variants are present.

It became clear that we were dealing with two reactions. In the first, $P^{31}O_4^{---}$ is combined with a neutron to give $P^{32}O_4^{---}$. This is followed by the second reaction in which $P^{32}O_4^{---}$ decays to $S^{32}O_4^{--}$ with the emission of a ß⁻ particle. Here we show that the first step is catalysed by an enzyme, which we characterise as neutron transferase. The second step is spontaneous in the present instance, but it is possible that enzymes exist for this step as well.

Neutron transferase is found in small lipid vesicles which have a very high density (>3). This is largely contributed by special lipid molecules that contain a large amount of lead. One of these components has been purified; it is hexadecanyl triethyl lead, $C_{16}H_{33}Pb\,(C_2H_5)_3$. These vesicles, or plumbosomes as we call them, contain all of the neutron transferase of the cell. We have also identified two transport enzymes in the plumbosome. One directs the inward flow of phosphate ions, the other specifically extrudes SO_4^{--}. Thus the radioactive phosphorus does not mix with the phosphorus pool of the cell and, in particular, is not incorporated into DNA.

We do not understand the need for the lead-lined cellular compartment. Most of the ß⁻ decays will go through the cell and will not result in any DNA scission. Our conjecture is that originally tritium was produced in such plumbosomes by an analogous enzyme, in which case the lead lining was necessary to prevent the shorter range particles resulting from tritium decay from severing the DNA.

We have partially purified neutron transferase and found that it contains boron.

Magazine

False starts

Tour de Farce

Sydney Brenner

Readers of *Noah's Arkeological Notes* do not have to be reminded that this year, 2453 on the old calendar, is the 500th anniversary of the publication of the famous paper on the structure of DNA by Watson and Crick. Only one copy in the original paper form has survived, but the Shanghai Institute of Bio-Historiography has made available replicas printed on titanium sheets to guarantee its preservation. The Institute is devoted to the reconstruction of the early history of DNA research, a task of immense difficulty, since so few documents have survived from that period.

This was partly due to increased use of electronic communication on inferior equipment in the latter part of the 20th century, but mostly the result of the disaster of 2020. In that year a bacterium, *Supercella # 681*, engineered for superior qualities of cellulose digestion at temperatures ranging from 0° to 120°C, was stolen from the laboratories of Svensk Gensk and inadvertently released into the environment when the thieves were apprehended for speeding. The bacterium spread rapidly through the world, carried in books and newspapers of air travellers, destroying every piece of paper it encountered and wiping out whole libraries. It was discovered much too late that cigarette ash contained a potent inhibitor for the bacterium. Most of the surviving documents came from the libraries of the few inveterate and careless smokers left at that time, and from occasional lucky finds.

One such find was a metal box of documents discovered during the recent excavation of the ruins of Liverpool Street Station in London. These shed considerable light on the early history of genome sequencing. As everyone knows, today DNA is sequenced using the meson probe nanoscope which was invented in the middle of the 22nd century (old style).Today's versions are very sophisticated and single molecules of large genomes can be scanned in microseconds and small ones in nanoseconds. In fact we now store sequences in the DNA molecules themselves; we can extract the sequence very quickly and quantum computers make light work of the analysis. It is hard to believe that huge enterprises were required to obtain such sequences and that the description of the sequence was stored on primitive magnetic or optical spinning discs.

The Liverpool Street Station find also reveals that there were very early Chinese connections to human genome sequencing as had always been suspected by our historians. For example, there are documents indicating that a very important contributor in the early days of the project was one Lee Hood, and although Hood is not a Chinese name it is likely to be a corruption of something like Hong, as it was common to anglicise names in those days. The documents also show that the most significant contributors were four scientists, Sulston, Hinxton, Waterston and Washington, the first two in England and the last two in America. A minority believe that these are place names but that seems most unlikely. Professor Won Ton has suggested that the 'ton' may be an honorific title appended to the names of those who had carried out 100 megabases of sequencing. He has noted that the word ton, originally a weight measure, was widely applied at the time to attaining a speed of 100 miles an hour on a motorcycle.

Another name that appears in the documents is Cantor. This was found only in its hand-written form and may really be Canton, possibly indicating the ability to do 100 megabases of sequencing, and pointing again at a Chinese connection. The most exciting find are documents proving that the first large-scale factory was actually constructed by Perkin-Elmer and Venter in 1999. There is considerable controversy about these names. Thus everybody has noticed that Venter does not have the ton suffix and many believe that his contribution must have been negligible. However, it has been suggested that the ter suffix may have been derived from tera, and given to those who had completed a million megabases of sequencing. This is possible, since the factory was capable of producing 100 megabases of sequence a day, and a terabase could have been achieved in 30 years, or even less if the factory had been expanded. Perkin-Elmer has more mysterious origins. One scholar believes that Perkin may be a corruption of Pekin, itself a corruption of Beijing, and thus another sinosoidal connection. Elmer is more difficult. It has both Hebrew and French overtones and the most ingenious explanation is that this should be read as Pekin-el-mer, and refers to San Francisco, which at the time was also referred to as Baghdad-by-the-Bay.

The documents finally eliminate the commonly held view that the sequencing had been done by the great Watson himself. They also show that the concept of factory sequencing had been proposed by Walter Gilbert in the mid 1980s, and although his first name has the significant ter suffix, there is as yet no trace of the related accomplishment.

Magazine

False starts

To sleep, perchance to dream

Sydney Brenner

Somebody asked me the other day whether fish sleep. My response was: "How can you tell?". I have spent a good deal of time in aquaria watching large lugubrious-looking fish lying motionless in a tank. Even though their eyes are wide open, they could be asleep for all the notice they take of their surroundings. There are also fish that swim endlessly and pointlessly; for all I know, they swim in their sleep. Even harder to know is whether fish can dream. Yet it is probably dreaming that is the important process and sleep may just be a way of achieving dreaming without unnecessary distraction.

We humans sleep and we dream. Our waking hours have produced many interpretations of the dream experience. Humans inhabit two worlds: the waking world — solid and continuous but, at the same time, narrow, routine and repetitive — and the dream world —fantastic, fleeting, and for many, an escape from the bondage of reality. In the dream world we can do amazing things and we are reluctant to consider this world as purely illusory. That is why the interpretation of dreams has been so important in many branches of psychotherapy; the belief that there are latent truths hidden in the manifest nonsense of dreams is hard to give up.

In a paper in *Nature* in 1983, Francis Crick and Graeme Mitchison proposed a functional role for dreams. They suggested that the function of dreaming, which occurs during REM (rapid eye movement) sleep, is to remove undesirable modes of interaction in networks of cells in the cerebral cortex. Their postulate was that this is done by a reverse learning process, such that the trace in the brain of the unconscious dream is weakened and eliminated. In an accompanying paper, John Hopfield and colleagues showed that artificial neural networks can benefit from dreaming. In such associative systems, spurious memories are created at the same time as real ones during the learning process. These can be minimised if an unlearning process, which is similar to the learning one, but with the sign reversed, is applied with noise as an input. Of course, the machine does not dream any more than it thinks, but if complex associative systems require continual cleaning up, then it is the process that is important and it is a secondary feature as to how it appears to us in our consciousness.

But why do we remember some dreams and not others? It could be argued that those we remember are the ones that we think of as not being totally spurious; they seem to have some significance. Their apparent significance may subsequently be completely dispelled in the cold light of our day-time existence. But sometimes, as has happened to me, remembered parts of a dream can lead to other thoughts, more useful and more rational.

The Homeric poets took dreams as objective facts and dreams had a standard form in their writings. There is a visit by a dream figure who enters the room to deliver a message. The dreamer is passive but he sees the figure and hears the voice as outside of him. Waking dreams or hallucinations were treated in much the same way. Of course, these were constructions that were conditioned by the culture of the time, where everything was believed to be under supernatural control and dreams were one way of communicating with the gods. I have never had dreams like this. All my dreams have been of endless, tortuous journeys though rooms, tunnels, up and down stairs (*pace* Sigmund) or have been completely abstract, like Kandinsky paintings. Some are in colour but when I was young most were in black and white; perhaps it was only after Technicolor became more widespread that dreams appeared in full colour to me.

I can write and talk about my dreams just as I can write and talk about my thoughts. In a curious way, dreams and thoughts are related. Both are activities of the brain that come into consciousness. Dreams, are fleeting and nonsensical ideas on the way out; thoughts are persistent and rational ideas on the way in. Both can be clothed in words or pictures or sounds.

If it is true that unlearning is mechanistically the reverse of learning, and if unlearning requires a special input (noise), the role of sleep becomes understandable. It is there to switch off all structured input while the reverse gear is engaged. If that didn't happen, we would unlearn everything we learnt, spurious or real. That this process manifests itself in the form of dreams in humans is neither here nor there.

I can now attempt to answer the question we began with: do fish sleep? And do they sleep to dream? The answer would depend on how much impinges on their brains and how much they have to learn each day. If it is a lot, they would need to have an unlearning activity period and they might need sleep to achieve it. I suspect they only need a short nap, because life is much the same day in, day out. But at least they don't have to attend lectures, for, at last, I understand why I find some lectures so irresistably soporific: I need the sleep to unlearn all the rubbish I heard during the lecture.

Magazine

False starts

Destiny rides again

Sydney Brenner

All meetings on the human genome include at least one talk, and often an entire session, devoted to discussing the ethical, social and legal aspects of genome research. The questions are always the same. If it is true that we can read the futures of people from their genes, should we be doing genome research? And, if we are going ahead anyway, what will be the consequences for society?

Some years ago I compared genomics to astronomy and thought it should be called genonomy. Like astronomy, genonomy is an observational science and mapping genes in the genome is not unlike mapping stars in the heavens. Both activities are similar in that they allow us to look backwards in time and offer possibilities for the reconstruction of the long vanished past — cosmology for the physical world and evolution for biology.

It has only recently dawned on me that other parallels may exist as well. Astronomy is a science that generated two different theories about its observations. One, cosmology, deals with esoteric matters, such as the beginning of the universe, black holes and the birth and death of stars. Even if they get things wrong sometimes, the practitioners are constrained by laws of physics. The other theory is astrology, which some people find much more down to earth, and which proposes that the destinies of humans are controlled by the stars, and that events in individuals' lives can be predicted from the conjunctions of constellations at the times of their birth.

I was about to write that genonomers should be careful to avoid creating a genology equivalent to astrology, when I realised that it has already happened. It was called eugenics and was based on the belief that the causes of social illnesses, such as poverty and crime, were to be found in the genes of people, and that the cure for such diseases could be effected by genome eradication. That this could be the case, seemed as plausible to our Victorian predecessors as the theory that the stars controlled our lives must have appeared to early astronomers.

Of course, we can argue that genes undoubtedly specify the structure and function of organisms and that stellar determination of our destinies is total nonsense; but in actual fact there could be a connection — day and night, the ebb and flow of tides, and the succession of seasons are all caused by the motions of heavenly bodies and all undoubtedly affect us.

Most of the problems in genonomy stem from a relatively new subject called predictive medicine, which is, if you like, the modern form of genology. Although there are genetic diseases for which clear cut predictions can be made from the genome, there are others which can only be probabilistic. While the bad news is that some common complex diseases show 50% concordance in identical twins, this is also the good news, in that there is a huge environmental contribution. The main difficulty in this area is that probability has no meaning for the individual. If you tell the man in the street he has a 60% chance of getting a disease, he will ask you whether he is in the 60% or the 40% class.

By contrast, social institutions, such as governments, insurance companies and large corporations, live by probabilities and do not really care about individuals. This is the singular dilemma of human genetic studies: looking at the genes is different from measuring blood pressure or doing urine analysis. These are products of both your genes and the life you have led, whether you have eaten too much or too little, or have been too stressed or too relaxed. But the genes are forever, and the idea that we could cast a 'somoscope', and say that the conjunction of a polymorphism in gene 47,384 with allele 8 of marker D-878 makes it likely that you will be both a first class jockey and a concert violinist, is ridiculous in the extreme. And yet some people insist that we could do this and clone such genomes, so that everybody could win the Kentucky Derby while playing a Mozart violin concerto.

We also have to deal with the lawyers. In America, where everything is settled by litigation, and increasingly so elsewhere, we can imagine the following situation. A man is denied health insurance, promotion at his work and his wife obtains a divorce on the grounds that his somoscope shows he has a probability of 60% of a heart attack before the age of 45. Following legal advice, he sues his parents for giving him bad genes and exposing him to the terrible life he has to endure. They should have known this, he claims, and taken care of that zygotic event. Had they done so, however, the plaintiff himself would not have been cured of the genetic stigmata; rather, he would be somebody else, and as the law only recognises persons and not genomes there would be no case to meet and the judge should throw the case out of court.

Last but not least, we have to remember that the bad genes singled out today were good genes a long time ago when they were selected by nature for our survival. The trouble is that nowadays winter never comes to Southern California.

Magazine

False starts

Refuge of spandrels

Sydney Brenner

There is a strong and widely held belief that all organisms are perfect and that everything within them is there for a function. Believers ascribe to the Darwinian natural selection process a fastidious prescience that it cannot possibly have and some go so far as to think that patently useless features of existing organisms are there as investments for the future.

I have especially encountered this belief in the context of the much larger quantity of DNA in the genomes of humans and other mammals than in the genomes of other species.

Even today, long after the discovery of repetitive sequences and introns, pointing out that 25% of our genome consists of millions of copies of one boring sequence, fails to move audiences. They are all convinced by the argument that if this DNA were totally useless, natural selection would already have removed it. Consequently, it must have a function that still remains to be discovered. Some think that it could even be there for evolution in the future — that is, to allow the creation of new genes. As this was done in the past, they argue, why not in the future?

Some years ago I noticed that there are two kinds of rubbish in the world and that most languages have different words to distinguish them. There is the rubbish we keep, which is junk, and the rubbish we throw away, which is garbage. The excess DNA in our genomes is junk, and it is there because it is harmless, as well as being useless, and because the molecular processes generating extra DNA outpace those getting rid of it. Were the extra DNA to become disadvantageous, it would become subject to selection, just as junk that takes up too much space, or is beginning to smell, is instantly converted to garbage by one's wife, that excellent Darwinian instrument. But even this fails to convince.

It was therefore with great interest that I belatedly read Stephen Jay Gould's paper on *The exaptive excellence of spandrels as a term and prototype*, which was published in the *Proceedings of the National Academy of Sciences, USA* last September (**94:**10750-10755). The paper has an important message and I strongly urge my readers at least to look at it, even if all the words in it can't be understood. I offer this brief summary as a guide.

The term spandrel originates in architecture and is used to describe spaces left over as a consequence of some other design decision, such as the triangles that remain behind when a rectangular wall is pierced by an arched opening. No self-respecting architect would simply leave such spaces, especially in a grand cathedral with a rich patron. Instead they would be decorated, as is the case of the four pendentives under the dome of San Mario in Venice, which are decorated with the four evangelists. This example is a good one, because the historical sequence of events is known. The spandrels are the consequence of a structural design decision, a by-product of placing a dome on rounded arches; three centuries later, mosaicists decorated these spaces. Thus spandrels are not primary adaptations but, because they can have later uses, they become, in Gould's terminology, exaptations.

In biological systems, we are confronted with the final result and we are required to distinguish between primary adaptations and historical products, some of which may have become co-opted for use. We need to separate the survival of the survivors from the survival of the fittest; as Manfred Eigen pointed out, the former is an historical inevitability whereas the latter involves choice and has a value function governing that selection. Gould points out that we can make the separation in several ways by analysing the historical evidence or by comparing many examples of the same structure.

While in the case of San Marco's pendentives it is clear which came first, this may not be always the case. For example, had the architect, in the same conception, provided both the main design and the use of the triangular space, it would be hard to separate the spandrel and its use from the primary construct. What can be shown to be unlikely is that the entire design was generated for the purpose of the decoration and that it is the dome that is the spandrel. This is because there are many domes on arches without any decorations. Being aware of degenerate organisms, however, we'd need to show that these unadorned specimens are not spandrels that were originally decorated but had their decorations removed at a later date.

I suspect that the term spandrel will not survive. It is both too fancy and not catchy enough. But the main difficulty with Gould's article is its anthropomorphism. We are constantly urged to explore the intent of the architectural designer, to distinguish between what he wanted and what he had to live with as a secondary consequence. There is too easy a transition from the analogy to the Great Designer and his intentions.

We should be looking at the problem directly and be studying the grammar of systems that can evolve complexity by natural selection rather than seeking the comforts or discipline of analogies. These morsels could become wastrels.

Magazine

False starts

A votre sanity

Sydney Brenner

Some years ago, I returned to England from Japan and found that I could not hear properly with my right ear. In a few days I had become completely deaf and could only converse with people in profile. I thought that this was a case of simple blockage due to my oriental genes for waxy ears, and I went across to the hospital to have my ear unblocked. The doctors took it much more seriously. They gave me a large number of tests and admitted me for yet more. I was told that I should face the possibility that my deafness would be permanent.

This was worrying, but I was consoled by my knowledge that there are several advantages to being selectively deaf. Some years ago, when I worked in France, I found feigned deafness to be extremely useful in dealing with requests for payment. I could never deconstruct $4 \times 20 + 10 + 7$ francs from rapid verbal demands, but sudden deafness, accompanied by much handshaking, always succeeded in getting the number written on paper and, at the same time, earned the sympathy of elderly ladies passing by.

A similar strategy helped me get into the lab at the Institut Pasteur to work at night. In those days, one could not enter the institute after hours except with the express permission of its director. As this permission needed a special interview with the director, and since it took six weeks to get an appointment to see him, I clearly had to find another solution to night working during my four-week stay. Feigned deafness was the answer. I approached the gate with an angelic smile and a cupped hand to one ear, while offering much handshaking and the odd French phrase such as "*coup d'état*" or "*tête à tête*". Eventually the concierge stopped yelling "*interdit*" to me and just let me in.

I have also noticed that when people think you are deaf they begin to speak not only loudly, which is understandable, but also slowly and in simple language, like some colonial administrator speaking to an uncomprehending native. If one happens to be an uncomprehending visitor, this can be helpful.

But I digress. The next stop for me in hospital was to have a brain scan. A doctor told me that he was pleased because he found nothing there. I was placed on steroid infusion and allowed to move around as long as I took my drip and its stand with me. As my lab was in the same building as the hospital, I often disappeared at night, much to the consternation of the nurses.

Still having a lot of spare time on my hands, I spent most of it reforming the health services. As there is much concern today with problems of the healthcare system, its planners may be interested in some of my proposals. More sophisticated readers will recognise that many of the ideas, now about ten years old, are already being implemented.

The key, I discovered, is to convert the health care system from one controlled by demand to one governed by supply. This was much in accord with the economic ideas of the day, and the approach has wide applications.

To give one example, a national committee of experts would decide how many deaths should occur in the next year from cardiovascular diseases. These would be allocated on a first come, first served basis. Alternatively, a monthly quota could be given to local or regional committees, with public representation, charged with making decisions that balanced need and availability. There could even be an appeal process. This simple scheme would have numerous advantages, but the main one is that it would provide an easy way to improve health care as these quotas for disease could be progressively reduced in the course of time. Some diseases might even be eliminated eventually. And medical research would face new challenges, such as finding new causes of death.

Another application of the concept is in the effectiveness of hospital stay. All that is needed is a decree that hospitals were never intended as places for dying, a function more properly carried out at home or in the street. Thus, before admitting any patient, the hospitals would require a 'life certificate' from doctors to ensure that the patient would definitely recover. Naturally, there would be an opportunity to obtain a second opinion.

The statistics would show a remarkable improvement. In addition, there would be new opportunities for the insurance business, as doctors would want to cover themselves from suits brought against them by hospitals.

There are many other possibilities for simple administrative solutions based on sound economic principles. I will one day disclose my plan for privatising government including its military arm, but here I need only tell you about Kagoshima. This town has an active volcano, and once, speaking to a senior administrator at the university about the problems caused by the smoke and dust, I hit on the perfect solution. "What you need to do," I said, "is to go up the mountain and place a big sign there saying "NO SMOKING". Were the volcano in France, the sign would say "ALL SMOKING IS FOBIDDEN, EXCEPT THAT WHICH IS EXPRESSLY PERMITTED BY THE DIRECTOR".

Magazine

False starts

Only joking

Sydney Brenner

I have always wanted to invent the perfect practical joke. All jokes are based on making a shift in the assumptions of the listeners and then guiding them by sheer force of logic to consequences that are so ludicrous that the real world can only be restored by laughter. Thus: two Martians met in the street, and one said, "What's your name?" The other replied, "29876 – 82", to which the first said, "Funny, you don't look Jewish."

Practical jokes require more than merely telling because they include performers and often very elaborate props and settings. There is a script, which is known only to the prime actor and which, by logical extrapolation, commands the participation of others.

Since a practical joke is run in real time, the laughter at the end is usually at the expense of the unwitting actors. Many practical jokes are extremely crude and can often be cruel, especially those that involve a large number of actors and one victim. These are designed to display the superiority of the perpetrators. The perfect practical joke should have an economy and convey enough of the conjurer's art so that nobody is totally dismayed.

An excellent example with some of these features was carried out in Cambridge by an undergraduate. Noticing some workmen digging a hole in the street he went and told them that a number of students dressed as policemen would shortly arrive and tell them to stop their work. He then telephoned the police informing them that a group of students dressed as workmen were digging a hole in the street. Together with many passerbys, he enjoyed the ensuing confrontation turn into realisation. I have not met anybody who actually observed this and so it may only be a theoretical joke, but it it is certainly both economical and artful in concept.

I once quite spontaneously performed that sudden shift which can lead everybody to accept what cannot be true. I was visiting the W--- Pharmaceutical Company in Japan and at the end of the tour I was taken to a meeting room where everybody had gathered. This company made a Japanese herbal remedy concocted from fermented garlic, which was widely used. It was called something like Lycopentane, which sounds like lighter fuel for werewolves, and was so vile tasting that it had to be taken in gelatine capsules. The dose was large, however, and the capsules could not be filled and sold without leaking, so a kit was provided with a dropper bottle and empty capsules.

I said I would like to try the remedy and with much amusement a kit was brought in. I filled a capsule and swallowed it. As it went down, I gave a strangled cry, followed by a gurgle, rolled off the chair and lay motionless on the floor. Through one half-opened eye I observed the reactions of my hosts. They were thunderstruck; the blood had drained from their faces and in the few seconds that I lay there, I could see running though their minds questions such as how to dispose of the body and what to do about my colleague who had observed the event, also with surprise.

The laughter when I rose from the floor was almost hysterical, and, in the end, everybody enjoyed themselves. I am quite famous in Japan for this and every now and then, somebody comes up to me, shaking their head, nudging me and saying "W--- Pharmaceutical Company."

I also consider a signal triumph an occasion on which I turned a practical joke on Max Delbruck. He was a great player of practical jokes, arranging for people to be invited to lectures and then embarrassing everybody. My chance arose after I had been invited by friends to talk at CalTech, where Max then was. On accepting, I said I would prefer to talk to a small group, but as it happens, this was unknown to Max.

When I arrived, I was carefully taken to Max's office, where a small group of people had assembled.They guided me to a small seminar room, where another two or three people were waiting, and everybody sat down. I assumed that my friends had arranged the small seminar I had requested, and without further ado, I began to talk. I noticed there were signs of dismay, and Max stood up, saying he was going to look at the notice board to check which room had been reserved for the talk.

Though a crack in the door, I noticed that Max was just standing there, and I realised what had happened. A grand lecture had been arranged, and somewhere there were 300 people patiently waiting for my arrival. Seizing the opportunity, I immediately increased speed, took off my jacket and began to settle in for a full hour. Max returned, puzzled by what he should do next; the looks of dismay had turned to panic and people had started to signal to each other.

Eventually I had to be stopped and the small party made its way to the large lecture room where Max merely signalled me to talk with a limp wave and no introduction. I had turned the joke, but of course I didn't let on that I knew. And every question asked of me that might test this, I answered completely ambiguously. This was perfection, as some people knew that I knew, but Max did not.

Magazine

False starts

Prescience

Sydney Brenner

Close to forty years ago, my senior colleague, Leslie Orgel, had the perspicacity to invent two novel disciplines, astrobotany and theochemistry, which he thought might be with us by the end of the century. I cannot remember what he wanted to include in these areas of research, but I want to report that one of these is flourishing now and that the other will soon appear.

I only recently heard that NASA has already set up an Institute of Astrobiology. I was most relieved to discover that this is not a real Institute orbiting in outer space, but rather a virtual institute composed of a number of different earthbound labs, all interested in the pursuit of extraterrestrial life. Keeping the institute dispersed in this form will clearly make it much easier for groups in other galaxies to join at a later date, should they exist and should they be interested in terrestrial life.

Astrobiology used to be called exobiology. NASA presumably changed the name to avoid confusion with dermatology, and also because after the moon was found to be lifeless, there was going to be a long wait until they got to other places. Mars still looks promising even though not much was found on the last mission. What is exciting is the growing realisation that our terrestrially-bound bacteria may provide guidance to the range of habitats compatible with life, at least as we know it. Thus the fact that there are bacteria that grow perfectly happily in boiling sea water at the bottom of oceans, or avidly consume carbon monoxide on the verges of motorways, widens the possibilities considerably. There is bound to be even greater variety among the microorganisms that we cannot yet cultivate. Indeed, when the earth was very young and there was no oxygen in our atmosphere, it is likely that a *Stinkococcus thermophilus* flourished in the boiling pools of sulphides. Perhaps cysteine and methionine are molecular relics of past thiochemical times. By counting us in astro-, the scope of astrobiology takes on a wider field and will certainly be more productive.

Compared with thiochemistry, theochemistry is a much less developed field and is still possibly a prescience. Perhaps I should be writing on it for our planned companion journal, *Future Biology*. This should not be confused with *Biology Futures*, which we are also contemplating publishing and, in case this puts ideas into anybody's head, we have also reserved the titles *Derivative Biology* and *Biology Derivatives*.

No Institute of Theochemistry has yet been set up and, of course, it would not be real, nor even virtual, but imaginary, as befits a complex field. The major scientific problem that confronts this field stems from considerations of how souls enter new human zygotes. The concern is whether individuals produced by cloning would have souls. Secondary questions, such as whether or not clones would also have the same soul, can be dismissed for the moment, because a soul might well behave like the immune system, and be different in each clone, provided that they were not made from lymphocytes.

Our first job in this field of soul migration and implantation, is to get rid of all the woolly thinking that has confounded the field for centuries and ask sensible questions which can be answered by experiment. Thus we think it unlikely that souls enter by diffusion as they would be too dilute. There must be a specific receptor and possibly an active transport mechanism. If so, there would be genes encoding these proteins and mutations in these genes would produce a soulless phenotype. All of us know candidates for this serious condition, but until now, a genetic basis seemed out of the question because it was a laughable proposition that the soul itself should be encoded in the genome. The idea of a human receptor neatly circumvents this difficulty and also explains why most animals and plants do not have souls. Perhaps dogs got the receptor from us by horizontal transfer via a retrovirus to which cats are resistant.

One can now see that a lot depends on when the receptor is expressed. If it is expressed only after, and as a consequence of, sperm entry, human clones will have souls because, in cloning, we simply replace the zygotic nucleus of a fertilised egg with a somatic nucleus. However, it is very bad news for parthenogenetic females who would be completely defective in natural souls, and who would require genetic therapy. The field is very promising.

Of course, all of this could be taking place at a much lower level. Readers will know that Roger Penrose believes that consciousness is a quantum mechanical phenomenon. We should keep an open mind about the subject and perhaps we should be thinking more about soulitons. Indeed, I have begun to consider that there may be a new field of theoretical physics concerned with quantum levity. I have got as far as postulating that the forces may be mediated by a new particle called a leviton. It will not have escaped the attention of readers that there is a connection between these particles and the genes for soul receptors and permeases.


Loose ends
by Sydney Brenner
1999

Magazine

False starts

The seven good byways of science…Publishing

Dear Sofie,

No, I don't at all mind you writing to me. I have nothing much to do these days and helping you is a pleasure and not an imposition. Most people will think it a pity that you have decided that you don't like doing research just after getting your PhD, but it is much better to make this decision now rather than incorporating it into a mid-life crisis in 20 years time. I don't fully understand the reasons you offer, especially the one about the music on the radio in the graduate student's lab, but I agree that a strong and sensitive girl needs something better than a boring postdoc in a unexciting place.

One suggestion I can make is that you try scientific publishing and, in particular, you should consider journal editing. There you will find many people who made the same decision to leave science and work in the exciting area of knowledge transmission, thus benefiting science in two ways.

You will learn that journals are solely responsible for the very high standards of judgement of intellectual ability that we enjoy today. Many decisions affecting the careers of working scientists are now left in the capable hands of a choice set of journals, thus allowing us to dispose of all those wasteful appointment and promotion committees. You will also meet, and have daily encounters, with an extraordinarily important group of scientists who constitute invisible — but not inaudible — colleges in the different disciplines. These politburos perform the difficult and onerous task of guiding both the science and the scientists in the proper directions and will help you to decide what is interesting, important and credible.

The development of this area of para-scientific activity can be attributed partly to growth in the numbers of journals, but largely to the discovery that editors do not have to read the papers submitted to them. It was different 40 years ago when I dabbled in journal editing. Then it was felt that editors had to be working scientists and understand the problems posed, the methods used and the answers found. In fact, there was a rule that whereas one editor could accept a paper, it required the concurrence of two editors for its rejection.

I developed several skills in this work. One was how to write letters breaking the bad news gently to authors. Phrases such as "the paper is far too long for its definitive content" survive to this day, I believe. I was never allowed to add that this content tended to 0, nor the suggestion that the length be increased by a factor of three and the paper submitted to a rival journal.

I also became sensitive to fraudulent claims and, in one case, suggested that authors carry out an additional experiment, which I knew could not work for subtle reasons. When the amended manuscript was received in the office with the bogus experiment faithfully executed, I sent a telegram informing them that I had made a dreadful mistake and hoped they had not followed my advice. All we then needed to do was to send the paper back to them.

Another important skill I acquired was that of translating Japanese English into real English, learning, for example, to apply what I called the prepositional calculus to sentences such as "10 ml of medium was added with 5 μg/ml tryptophan". I also knew when "varid" was "valid" and not "varied" and when "morecle" was "molecule" and not "miracle". In order to teach novices these fine distinctions, I urged them to consider the following restaurant notice: "Owing to lack of ram, there is no rack of lamb."

I learnt, too, how to deal with referees but never solved the problem of the referee who clung to manuscripts for months beyond the deadline and failed to respond to letters, telegrams, telephone calls and reports to the chairman of his department. Some people entertained the thought that he was deliberately trying to delay publication of the paper, presumably because he was doing similar experiments, but I thought this most uncharitable and preferred to believe that he subscribed to the great principle of never doing today that which you can do tomorrow.

Today, things have changed and everything is simpler. All you will have to do as a journal editor is to read the title, which should tell you what the paper is about. Good titles need to be in the declarative, such as *'Nox-1* is a regulator of the *dor* and *nob* genes, and is activated by the *bang* kinase family". Next, note the author's address to check that the paper comes from somewhere good rather than from a place you have never heard of. Sometimes authors give lists of referees they want or don't want to look at their paper. If they don't want their paper seen by anyone you recognize, it can't be much good. If the paper doesn't meet these standards, reject it with one of those standard letters you are bound to have at your disposal; otherwise send it out to referees, remembering that they are there to help you and not the authors.

I hope this helps you in your career choice. Do let me know how you are getting on.

Your ever-loving Grandpa Syd

Magazine

False starts

Remembrance of things past … Reading

Sydney Brenner

For more than twenty years, I shared an office with Francis Crick, beginning in one large room in the Austin wing of the Cavendish Laboratory at Cambridge University, where we also had five other people at their desks and, for a short while, some of our lab dishwashing. In 1959, we moved to a small room with two desks in a hut and this was followed by a succession of two other offices in the MRC Laboratory of Molecular Biology.

I am a paper hoarder and, with each of the moves, I would sweep everything into cardboard boxes that I always promised myself I would unpack and sort as soon as I had settled in the new office. But I never quite accomplished this. This collection of boxes, now alarmingly large, is still with me, partly in storage, and often in the original boxes and folders, now brown and crumbling with age. It is there waiting for me to retire again so I can devote myself to putting my papers in order.

Among these papers are large items that have always surfaced to the top of the pile because they did not quite fit into the boxes. There is a copy of the map of the rII locus of bacteriophage T4, which once covered an entire wall of my room in Kings' College and a roll of drawings of all the possible ways the bases might pair in two-stranded, three-stranded and four-stranded DNA molecules.

There is also a large placard on which are emblazoned in large black letters the words: READING ROTS THE MIND. This appeared some time in the mid-1960s and for years was displayed on the wall behind Francis's desk where he could always be seen avidly reading everything he could lay his hands on. This is, of course, an exaggeration, because Francis also spent a considerable time talking to people; our office sharing was successful because I spent most of my time in the lab or in the coffee room, and used my desk and the blackboards in our office only for discussions with Francis.

I was asked the other day where the words on the sign came from. Although the message sounds like Dr Johnson, despite neither beginning nor concluding with 'Sir', I recently learnt that it had been invented by a friend, Christopher Longuet-Higgins, who was, at the time, a theoretical chemist and a good mathematician. He believed in the admonition and presumably thought that reading other people's theories would corrupt you and prevent you from thinking about your own.

However, biology is very different from mathematics, and reading is absolutely essential. It is a subject abounding with facts, all of which need to be known and understood. In our joint office there were to be found folders of reprints and notes on a large variety of subjects. The contents of the folder would be read and read and read again and notes written until the subject was mastered. Thus, I can remember — and indeed still possess — folders of papers on DNA winding, heterogeneous nuclear RNA, chromatin, the C-paradox, optic nerve regeneration, the papers of Hubel and Wiesel, computation theory, and so on.

Some of these bouts of reading actually resulted in new research and often, in Francis's case, in papers. After a long period of preoccupation with DNA winding, which involved not only a considerable amount of reading but also a voluminous correspondence with a number of mathematicians who had become interested in the subject, Francis produced a simple version of what he was working on with the title *DNA Winding for Bird Watchers* — an allusion to a friend of ours who was thought to be a suitable audience. I bet you that this is still in one of those boxes.

It was in those days that I discovered the best way of approaching a new subject, which I still use today. You go to a library with an exercise book and pick up the past five years of the *Annual Review of Genetics*, or of whichever area is the most relevant to you. Scan the indexes and you are bound to find at least one article that will introduce you to the area. Read it and note, in your book, the references that are the most interesting. (It is fatal to copy the review because you will never read it.) You have to select these references stringently because when you read them they will give you more references, and the amount of reading can grow explosively.

My readers, probably browsing this page on their screens, will find this all old-fashioned and will no doubt be able to tell me about more electronic ways of doing this on the internet. But all of that information is so ephemeral. It leaves nothing for one to worry about when one retires.

When Francis went to America, I salvaged everything from the office including the sign. In 1977, I visited him in his grand office in the Salk Institute. Every surface was covered with piles of books and folders of papers on neurophysiology, neuroanatomy, psychology — in fact, everything to do with Francis's new interests in the brain. The only thing missing was the sign, READING ROTS THE MIND.

Magazine

False starts

The seven good byways of science … Biotech

Dear Sophie,

The news in your letter did not come as a great surprise to me because I knew that, sooner or later, you would not be satisfied with working for Mangledprose Publications. Working on a journal also poses many problems, especially as even science is now succumbing to the postmodernist idea that everything is a matter of interpretation and that there is no single correct truth, but many, depending on readers' point of view, and perhaps also on where the writer works. Now it would be a happy state if this was earnestly practised, but the paradox is that this politically correct view is accompanied by the firm belief that the journal knows what's best for its readers. I cannot understand this view, which assumes that readers lack critical faculties and need the generous guidance of editors and referees.

What did surprise me in your letter was that, in going back to the bench, you had decided to join a biotech company rather than returning to the academic path. You should realise that these are prize postmodernist institutions, where appearance and reality have become intertwined. As I have never heard of Pharmacophormatics I assume that it is newly formed. It also sounds as if it follows the current fashion of providing an integrative view of the mass of data coming from the large number of genomic, and now proteomic projects, suitably annotated for use by pharmaceutical companies. Actually, when you come to think about it, these are the journals or, rather, the textbooks of the future. You see, Sophie, you have probably not made such a big leap.

As you will soon discover, a biotech company is formed for one purpose, which is to turn an idea into a concept. A concept can be sold, especially if there is a little science to support it. I have always believed that we should be working on resurrection, because it does not take much market research to see that this would have immense public appeal. Personally, I would love to come back in, say, 100 years, just to find out what later generations have made of the world. For the success of Lazarus Technologies, we would need some experiments that show resurrection is feasible — a proof of principle, as it is called. If one could resurrect a mouse for even as little as a picosecond that would suffice. Everybody knows that all that is needed to extend this into the microsecond range is a little more work and then it is only a matter of time before we have it working for minutes, days and even months. Here is a multitrillion dollar industry in the making.

And here is another. I noticed in the newspaper the other day that the wonder drug of our times, Viagra, has been associated with an increased death rate of elderly gentlemen from overexertion. It is clear that we may need an antidote and if I had the time and the money, I would be making it. It would be called Niagara. Is Pharmacophormatics interested?

Companies need a business plan in addition to their programme of research. I have seen many of these texts and have been tempted to send them for chemical analysis to discover what dope had been smoked by the authors. A business plan aims mainly at self-consistency; that is, the figures produced need to match the deconstruction expectations of the investors. Accord with reality is not really necessary, although possibly an advantage.

In true postmodernist style there are, today, three views of biotechnology: the view of Wall Street, the view of big Pharma, and then, of course, there is the truth. The initial investors are interested only in the story of the company; they need to convince a few other investors that they could build it into a company of large value and sell it to someone else, making a quick and profitable exit. I trust your company is going to do something simple, such as provide a useful service, and not claim to become a vertically integrated pharmaceutical company; most of the ones with this ambition have ended up as horizontally disintegrated companies.

You will be offered stock options as an incentive to work for the success of the company. Take them. I have spent years trying to find a way of providing an equivalent incentive for academic labs but have been frustrated by not being able to discover a financial structure for the scheme. The closest I have come to it is to have the head of the lab share his Nobel Prize proceeds with the stockholders in the lab. I can also see how this could be turned into futures.

I fear I have been too severe on this industry but, actually, you will find it most exhilarating to join a company right at its very beginning. It is like going to a new land and moving into a house with the painters and plasterers still busy and with the furniture undelivered. At the beginning, you will have a free and informal style of life. Enjoy it while it lasts. The fun disappears when the company acquires a marketing department.

Your ever-loving Grandpa Syd

Magazine

False starts

The march of thyme

Sydney Brenner

I am most honoured by your invitation to speak at this meeting of the Shanghai Institute of Bio-historiography. As many of you know, I work at the University of San Francisco de Crico, in that remote Pacific province of the Spanish Empire, Hispano-America, and I am interested mainly in the early history of plant genetic engineering, that obscure period covering the end of the 20th century (old style) and the beginning of the following century.

You are all familiar with the fact that very little documentary evidence has survived from this pre-electronic period, and that there is considerable confusion about the events that took place in those troubled times. I am happy to announce here that we have recently recovered a remarkable collection of documents from a deep wine cellar of the ancient Napa Institute of Molecular Oenology, now a Benedictine monastery. These throw much light on the history of this period and are the subject of my lecture today.

The genetic modification of plants and their introduction into agriculture began with a number of very primitive and crude examples in the last decade of the second millennium. Thus there were crops carrying a gene conferring resistance to a herbicide, a chemical used to kill other competing plants referred to as weeds in the typical derogatory language of those days; and there was an amusing tomato which had a gene modification preventing the softening that accompanies ripening.

These products were generally accepted in the country known as America, but this was not to be the case in Europe (now part of Greater Norwegia) or in the large island of Tasmania, then called Australia. Opposition mounted to these Genetically Modified Organisms, or jimmoes, as they later came to be called, and to food manufactured from their products. The foods were called Frankenstein foods, and I have been able to establish that Frankenstein was a very early genetic engineer who worked in the field of human beings but was not very successful as most of his products did not work properly. We have found several illustrations of these inept and unfinished offerings, which were used to inspire fear, especially in small children, and associating these images with bottles of tomato ketchup must have contributed to the terrible events that ensued later.

It is important to understand the political background, and the Napa documents are very illuminating in this respect. Political organisations had colour names in those days, and at the time we are discussing, a dominant group, called the Reds, was being replaced by another party, known as the Greens. The Reds were, appropriately, meat-eaters, and their demise can be clearly linked to disease that was called BSE, or, more popularly, mad cow disease.

It seems that BSE was caused by an infectious agent that had spread in cattle fed products from infected sheep. The Reds succumbed to this disease through the consumption of various food products made from beef. It seems that the Greens, who replaced the Reds, were vegetable eaters, were opposed in general to unnatural agricultural production and instilled in the public a fear of food made from genetically modified plants. People began to worry about a potential mad potato epidemic, or worse. Some governments banned the growing of genetically modified plants, others the importation of products made from such plants and there was widespread demand that foods made with these products should be labelled as such.

The opposition spread and became worldwide. By 2005 in the old calendar there were widespread food shortages, followed by supermarket lootings and social unrest. Government instability led to a second dark age, but this was quite brief and by 2030, most countries had been restored to normal with the rise of the Turquoises, starting first in the Black Sea area.

Today, of course, we enjoy the products of a wide variety of sophisticated GE (genetically enhanced) plants, such as self-peeling oranges, sighing willows and the salad tree, with several varieties of dressings that can be tapped like latex. All of these are the products of a technology that was kept alive during the dark ages by several important organisations.

There was one product that apparently escaped the strictures that were imposed on genetically modified food, and that was alcohol. It was not really a food but a kind of drug. Drugs such as insulin had been manufactured from genetically modified organisms for decades and had gained acceptance. As the NAPA Institute documents make very clear, the technology was maintained by companies working in an area that fused wine making and pharmaceuticals. This explains why grapes became the best understood plant of those days. It also explains many of the names of well-known companies in this field such as MonSante, Rhone-Plonk, Briskol-Myers, Roche-Shield-Lafitte and Marc, Sharpe and Dom. Lettuce raise our glasses to them.

Magazine

False starts

The seven good byways of science … Big Pharma

Dear Sophie,

I heard that your company had been acquired by that pharmaceutical giant, Portentis, accompanied by much rejoicing by your investors. I wondered if you might return to Academe, and was a little surprised when you told me that you had decided to join Portentis. Although I have never worked in a pharmaceutical company, being mainly and now increasingly at the other end of their pipelines, I have had a little experience of them. This has been largely as a spectator, and the few times I got into the court it was to pick up balls rather than hit them.

You will find it important to understand the nature of these enterprises. Although they believe they are acting in the higher interests of humanity, ensuring our health and welfare, they are not averse to the considerations of the financial resources of those who can buy their products. After all, they are under severe pressures from their investors to provide the best return on the large sums spent on drug discovery, research and clinical development. You do not make much money from malaria, but give them something like male impotence and they will rise to the occasion.

Their drug pipeline is sacred and this they guard as savagely as any oil potentate, constantly filling it at one end and hoping that enough will emerge from the other end to keep their stock price up. Any hiccup in the pipeline makes for a very uncertain future and generally leads the company to find a partner; each partner has the intention of gobbling up the good parts of the other, while shedding everything that is tasteless and inedible in the process. You have to realise that when this results in the loss of 4,000 people that is equivalent to having an extra billion dollars a year. That is almost as good as having a new drug — perhaps not a blockbuster but at least a chipbuster.

The second thing you will learn is that these giant organisations have deep management problems. Lyndon Johnson once said that he would rather have somebody in the tent, pissing out, than somebody outside the tent, pissing in. The trouble with the companies is that everybody is inside the tent, pissing in and doing a lot more besides. Not only is their static structure complicated, but they are forever reorganising themselves, wondering whether they should be based on disease areas, or technology or locality. They are intensely hierarchical, with a well-defined reporting structure going upwards from the coalface through supervisors, managers, senior managers, directors, and vice-presidents to the CEO at the very top. He also has a board to report to and the board has a Chairman.

I have observed that these channels act as modulators certainly of amplitude but of frequency as well. Thus a problem at the lower level is not actually solved but is polished enough to soften the bad news, and exported to the level above. When this process is repeated several times, it results in a bland product, unrelated to any reality. You will find that all decisions made at the top on its basis are not very good ones, because those at the top are unaware that any problems exist. The reverse process is similar. A clear enough command can be given at the top, but as it passes downwards it undergoes fragmentation and bits fall off and are lost, so by the time it reaches the bottom, where people have to do something about it, they do not understand it. In most organisations with a cumbersome bureaucracy, entrepreneurs will find short-cuts, but this is not possible in the unstable environment of big pharma because nobody is around for long enough at any job to find these noiseless channels.

This is apparent to any academic who collaborates with the industry. They begin with a few thousand enemies, the research department of the company, who believe that it is their money that the company is proposing to give away. To counter this, the academic needs somebody in the company to champion their cause. When, after lengthy negotiations with everybody, including the lawyers, the contract is finally signed, they may think they have reached the end and can begin research, but it is only the beginning, because the collaboration will need to be monitored and to an extent that is proportional to the sum of money given.

If you become a champion you will find that as time goes on you will vanish, either because you are successful and have moved up, or — most improbably in your case — because you have not been successful and have been moved sideways into technology acquisition or report writing. With this loss, the level of ignorance of those monitoring the collaboration rises abruptly and, of course, they too are soon on the move, so that in three years there is nobody that understands the project or why it was ever supported.

I could of course give you a more detailed guide to the tricky paths in your new terrain, so please give me a call. If I'm not in, the chances are that I've gone to the pharmacy for my prescriptions.

Your ever-loving Grandpa Syd

Magazine

False starts

O sole mio!

Sydney Brenner

In my last paper on this important subject, lack of space prevented me from enlarging on the question of the uniqueness of the soul. I hinted that one model, the one that I favour, allows for somatic rearrangements of the soul, permitting the emergence of individuality just like that possessed by the immune system.

Professor Dolcecaro of the Istituto di Immunologia in Pesto, has sent me a somewhat naive letter on this subject, proposing a very mechanical approach to this important issue. His view is that if souls could undergo rearrangement we would expect both inverted and deleted souls and, although he is prepared to leave the former to psychoanalysts, he wishes to assert prior claims to the latter, not only to the discovery itself, but also to any practical applications. I surmise that he has some special genetic therapy for deleted souls if, indeed, this unfortunate situation exists. However, he locates the soul quite literally in lymphocytes, and this is certainly wrong. As everybody knows, the soul is in the brain — at least, most of it resides there, although some pieces of it may be located in the heart, the intestine and possibly in the knee joint.

One should not think of souls encoded in DNA but, rather, distributed throughout our nervous systems. The cellular localization of the soul is still hotly debated; everybody is agreed that it is definitely to be found in neurons of the central nervous system but there are some who hold that it might also partly reside in glial cells. In peripheral locations it is also in neurons, particularly those of the sympathetic nervous system.

The comparison of the soul with the immune system is by way of an analogy and not to be taken too literally. Nevertheless, it is a good analogy and I am happy to say that recent research has allowed me to provide a more complete picture of the process.

All souls are used only once. There are what may be called ‘germ-line’ souls and their pristine structures enter the newborn by means of a special receptor, as discussed previously. These souls have a common part and a variable part and only the variable part undergoes rearrangement in the *n*-dimensional space of the brain, thus generating an individual, unique soul for each of us. It is thought that the common part of the soul resides in glial cells, where it is stable. However, there may be individuals in whom glial cells acquire neuronal characteristics and subject the common part of the soul to variation. This might explain the large number of abnormal states which, in pre-scientific times, were attributed to diabolical intervention.

Readers will note that the theochemistry of the soul is not compatible with some religious theories, although it will be welcomed by others. In particular, it rules out the return and subsequent transmigration of souls. Thus, the fear of ending up as a pig in Arizona can be dispelled. There has been a proposal to allow the common part to be returned and used again but this would require elaborate checking to verify that it had not been modified. Minor damage could be repaired but a special place would be needed for the consignment of irreversibly damaged souls. This idea is quite an old one but it seems to me to be unnecessarily bureaucratic and complicated, especially if there is an endless supply of germ-line souls.

A small boy has written to me asking where the store of souls is kept and in what form they are retained prior to use. In particular, he wondered if they are frozen or dried and whether they expired after certain dates and had to be thrown away. The interface between theochemistry and theophysics has only recently begun to be explored, and his questions cannot be answered in the form in which they have been put.

There are two theories at present: one is that souls are continuously created, thus ensuring a steady-state supply; the other, known as the ‘big binge hypothesis’, is that an infinity of souls was produced at one time and expanded to occupy the entire Universe. We could distinguish between these hypotheses by measuring the ages of germ-line souls; the latter hypothesis predicts that these would all be very old. Unfortunately, there is no rigorous way to perform these measurements but claims have been made — especially by Jurg and his followers — that all souls are very old. Indeed, the connections between modern theories of the soul and those propounded by the psychoanalysts is a very interesting line of research. One need only point to the relationship of the common and the variable part of the soul with the id and ego of Freud.

I trust that these modest contributions will stimulate others to take up this new and exciting field of research. Many of my predecessors in this field found it difficult to get their research published and several were subjected to censorship of the incendiary kind, which affected both their writings and themselves. I have to thank *Current Biology* for its enlightened attitude and for opening its pages to these recent advances in theochemistry.

Magazine

False starts

The seven good byways of science … The rest

Dear Sophie,

I was delighted to learn from your latest letter that you have decided to leave industry and return to a more academic life. I thought at first that you were going to say that you had gone into a more administrative position, either with some research organisation or with one of the foundations involved in research. So it came as a very pleasant surprise to learn that you have decided to teach science to young people. Politicians and educators are forever complaining that the young are not interested in sciences and technology but instead are either entering the safe professions of medicine and law, or taking up riskier, but potentially more profitable, positions in the financial services, such as trading in futures or derivatives. We really do need good teachers of science and it is not enough to hope that there will always be people such as yourself who have made the choice as a personal act of dedication. I once suggested that the solution was to pay teachers as much as we pay managers and administrators, which would improve matters overnight.

Having chosen teaching over research administration, I implore you to stick to teaching itself. That way you do not have to endure the climb through the jungle of management and administration. In science, and no doubt in teaching too, this largely consists of telling other people what to do rather than doing it oneself. As one ascends in the system, the iteration increases and one can find oneself telling other people to tell other people, who tell other people, and so on until one reaches the coalface. So busy are the people at the top that it is now impossible to make direct contact with anybody one step removed from direct activities. This is true for all the organisations I deal with — universities, industries or funding agencies — and doubtless for school teaching, too.

If you try to make direct contact by telephone with anybody these days, you are very likely to be confronted with a menu. Usually none of the possibilities offered fits your needs and the recitation of the menu usually terminates by cutting you off. If, by any chance, one option sounds suitable, it is often the entry point to an even more incomprehensive sub-menu. Assuming you eventually reach the correct extension, you will be told that Dr X is unable to take your call because he is either away at a meeting or engaged on another telephone call — and would you like his voicemail. I once took my revenge on the system by leaving a message, which went roughly as follows: “If you want to hear a message, press 1.” (Pause.) “If you want to hear it in French, press 1, in German, press 2, in Icelandic, press 3, in Etruscan, press 4, in English, press 5.” (Pause.) “You may return to the main menu by pressing 354.” My recipient actually performed the first two steps before he realised that something was wrong and that his actions had nothing to do with the subsequent events. This shows that it is easy to teach intelligent people how to do stupid things.

These days really important people, such as professors, have assistants. It is incorrect to call them secretaries. Dr X’s assistant does not work for her, but with her. Actually, most of the time, he is working against her. In many places, it is impossible to contact Dr X and all that one hopes for is that one can talk to Dr X’s assistant. However, with the rapid evolution of the system, reaching the assistant’s voicemail is the likely outcome. Of course, as all sophisticated people know, one should communicate by e-mail, but I have found that once the volume of messages increases, it becomes useless. The only advantage is that one can delete everything without bothering to read anything. I could never do this with letters for fear of throwing away a cheque that had been sent to me.

The art of management or administration consists, first, in not knowing anything about the area one is managing or administering as this could lead to biased judgement, and second, in having meetings which should, if everything is working well, produce only another meeting and not any definitive decisions. In a perfect world, the only decisions any meeting should agree to is the time and place of the next meeting, and also who should be invited. Under ‘other matters’ it would be proper to consider where to go for lunch.

At the very top of the management/administrative pyramid are the really important people. They all have an occupational disease that involves their hearing ability. They are not deaf but have an auditory opacity that filters out the semantic content of what other people are saying. I once proved this by the following conversation. “How are you, dear boy, how is your leg?” was the question to me. “They had to amputate it,” I replied. To which the response was, “Wonderful news, it is good to see how well you are doing.”

So Sophie, you see you have missed nothing and your path will, in the end, be more satisfying and more productive. Perhaps you may even one day return to research.

Your ever-loving Grandpa Syd

Magazine

False starts

Remembrance of things past … Writing

Sydney Brenner

When I was young and brash and generally ignorant, I found writing easy. I could dash off pieces entitled "Towards a Semantic Sociology" with no effort at all. This appeared in a student's magazine but fortunately did not achieve wide circulation and does not figure in my list of publications. I was eighteen and a committed logical positivist.

At an even earlier age, I won a prize for writing. An organization, the Sons of England, had an annual essay competition in South Africa and the schools chose their best pupils to enter it. My school did not select me, but I decided to enter on my own. The subject was "The life of Nelson". I repaired to the local library to read and, after being distracted by Lady Hamilton, learnt enough to produce an essay. To everybody's surprise, including my own, I won the competition and had much pleasure in receiving the prize — a suitably jingoistic book — from the irritated headmaster at a school assembly. The book has long since disappeared, but the essay and prize should be the first entries in my curriculum vitae.

Later, as my scientific career unfolded, and I began writing scientific papers, I found myself forced into a style of writing, that imprisoned me. All papers had to be set out formally with an Introduction, Material and Methods, Results and Discussion; one never, *never* used the word "I", but instead that grovelling euphemism "the present author," and instead of plainly saying that "the work of Watson *et al.* was a load of crap," one was compelled to write that "their experiments led Watson *et al.* to erroneous conclusions." Any thoughts one might have were labelled by others as "unfounded speculation," a tradition that continues to the present day and is carefully monitored by those unsung guardians of scientific integrity — the ever-watchful referees.

I found myself becoming increasingly constipated, my vowels refused to work and writing became more and more difficult. I thought that if I carefully chose the pen, the paper and the colour of the ink my problems would be over, but it didn't help and I simply became a stationery fetishist. For many years, I thought the stylistic constraint of writing scientific papers was the main reason for the loss of my youthful writing abilities, but I now realize there was another reason. I cannot write anything until I have everything clear in my head.

There still remains the difficulty of a good opening sentence and the impossibility of starting with the second or even the third sentence, but once that hurdle is crossed, everything flows onto the paper in long-hand, almost finished. In my youth I had much less in my head to rearrange, especially in subjects like sociology or Lord Nelson, so I could get them onto paper very quickly. With the loss of ignorance, my head became filled with more and more thoughts, and picking a path through this jungle became increasingly difficult. Perhaps, with age, this store will thin out and the old ease of writing will return.

Writing and talking are very similar in that both involve putting words together, but there is one difference: in talk one concentrates on what is being said at the moment, whereas what has already been said is gone, vanished; in writing, however, everything is there, with all its awkwardness, to confront you. I find talking very easy. I never use notes in seminars or lectures and all I have to be careful about is that I don't use the same jokes twice in the same place. I was told that Fred Sanger once expressed the view that I was bright but talked too much, but then he once described Francis Crick as "that chap who is rather keen on genes."

Language is a source of endless fascination for me. I enjoy all those strange conjunctions that one can create to escape from the confines of everyday existence. Thus it seems very reasonable to me that a New York delicatessen company, Cohen & Caruso, might have matzohrella as a product. There may actually be an ancestral genotype for the ability to compound words: my young grandson proposed Sosumi as the name of a Jewish–Japanese restaurant.

Naturally I make friends with other people who enjoy this kind of word play. Bernard Williams, the philosopher, and I spent many a happy hour inventing menus for astrophysicists, with such items as Toad-in-Black-Hole, and Pen Rosé wine, which would be offered in a club featuring live music from The Naked Singularity group.

We also established the Squeaky Cheese Press to publish books with special titles suitable to the subject or the authors. *Homage to Catatonia* was a psychiatry monograph, and *Daimons are Forever* was a text in Jungian psychology. A book to be written by two friends, one an ornithologist, the other an astronomer, was entitled *A Day with the Chicks; a Night with the Stars*. And most proudly we had: *The Turing Shroud: an Essay in X-ray Christology*. Alas, none of these books will ever be written, and especially not by me, because I have been unable to find the good first sentences.

Magazine

False starts

Sillycon valley fever

Sydney Brenner

Over the past year, and especially over the past few months, there have appeared intimations that the newest revolution in post-genomic biology is under way. This is taking the form of microarrays of nucleic acid molecules, or DNA chips, onto which complementary probes can be annealed. Their main application is in the generation of a very large amount of data on gene expression. The activity in this field is growing rapidly and includes companies making chips or making chip makers and chip readers, and companies selling the DNA or reagents or software.

I do not want to decry technical advances in biological research, nor do I want to retain old habits simply because they are old and I am becoming a sentimental old fool. But as one of the few voices from the pre-genomic era, and because the founders of any church know its defects better than all the new, enthusiastic converts, I am moved to say my piece.

Like many new vogues, the new revolution has its epicentre in California, although some minor eruptions in the vicinity of Boston have been recorded. It is all accompanied by many proclamations in Old Sloganic: such as, "Why study one gene at a time when you can look at thousands of genes under dozens of different conditions at the same time." There are new concepts such as 'self-organizing data' and 'emergent phenomena'. The main idea, if it can be called that, is to take millions of data points and put them through some computer program, sometimes called 'cluster analysis', and see what association can be found. Some have even hinted at Fourier analysis of the data.

But most iniquitously of all, one of the missionaries of the new field has stated that it will liberate us from the "shackles of hypothesis-dominated biological research." In plainer words, you do not have to think anymore to do research. Are we really about to enter the decadent phase of biology in which scientists will be unable to see what the problems are or, if they do, will be unable to formulate questions that could be answered, either by observation and measurement, or by intervention and experiment?

It is my view that you cannot study gene expression and make sense of the results without having an explicit theory about global aspects of gene regulation. We are told that when we study all genes we see many unexpected changes in expression, even of genes we thought to be the very epitome of constancy. Taking all these changes seriously, however, implies the hidden assumption that they have been fixed by natural selection and are optimal for that organism. If this were so, we can calculate from the data the evolutionary cost in control genes required to specify all of the combinations found. This is enormous.

Let me briefly sketch an alternative approach. Before we consider how genes are turned on and off, we first have to ask how the transcription resource is allocated to all the genes active under some given circumstance. Clearly, as specified in its DNA sequence, each promoter will have some affinity for the transcription complex. This can be adjusted by natural selection under standard conditions of growth so that the majority of genes making small amounts of message can access the polymerase in competition with the smaller number of genes producing abundant messages. Now, if a change in the population of messages occurs as a result of some change in the set of genes expressed, the absolute amount of RNA produced by any gene will change in response to the new competitive conditions set up. The changes do not reflect a new set of specifications for the genes, but arise automatically as responses to a global situation.

We can take this further and think of competition for RNA processing, for access to ribosomes, and so on. Thus I do not doubt the significance of all of these findings from the point of view of measurement, but I doubt their meaning for the biology of the cell, and whether they can be comprehended without a theory of the molecular ecology of the cell. We may also find genes which, although turned on in a cell, are unnecessary for the functioning of that cell simply because they obey a 'don't care' condition for that cell. Nature simply may not bother to turn them off, even though they are not needed, as long as they are doing no harm.

For survivors of the pre-genomic era, this approach will be very familiar: I now have the outlines of a theory that I can develop further. Moreover, I can construct critical tests for its consequences. Running more chips and having more data and more computer programs will not extract this theory because computers can't think. Sadly, human programmers are becoming like their machines. Perhaps what I can do with my approach is to find the critical genes to study and give the world a smaller chip with only a handful of genes. When next you hear "More is better", just remember that Uncle Syd says "The least is best." Let's get back to solving problems and providing answers to questions.

Magazine

False starts

Moron peer review
Sydney Brenner

It's true that I have written on this topic before but my knowledge of the subject as it relates to the problem of obtaining support for research was then based on second-hand information from other scientists. Thus, the picture I received of the NIH study sections was of groups who had managed to combine inanity with iniquity laced with ignorance. As this came from people who had been turned down by one or other of these study sections I thought there was a certain amount of exaggeration but, now that I have direct experience of the 'NIH system', I can confirm that everything I have been told is absolutely true.

A few months ago, against my better judgement, I applied for a relatively small grant to support some work on the pufferfish genome that might have some relevance to one of the many diseases that NIH is determined to cure. Also, against my better judgement, I took the advice of a semi-professional grant writer who criticized one section, where I simply stated that we would try an experiment which had never been done before. He insisted that I provide an example of what might be expected and, in fact, he found one for me, assuring me that without this, I could not expect to be funded.

After several months I received a notice that my priority had been assigned as 272, which I was told was dismal. Some weeks later I received a bulky document called a summary statement detailing the proceedings and the result of the peer review by the study section and enclosing a list of the members many of whose names were not familiar to me. Roughly speaking, they had come to the conclusion that although I had done a few things in the past I was out of my depth in the particular area chosen and although they admitted that I had some scientific expertise they felt that I should seek some help; all of this had conspired to reduce me to the 52.5 percentile rank.

In studying the document I noticed that I was much worse than that. Apparently, the section members assign scores from 100 to 500 based on scientific merit. This means you cannot do worse than 100, and so there are only four intervals and the midpoint is at 300, which means that with a score of 272 I was actually below the percentile rank assigned to me. This sort of arithmetic misunderstanding is common among biological scientists. Recently, at a meeting, a graph was shown with four points to illustrate the claim of a 10^4 dynamic range. As there were only three intervals, and the first point was close to the noise level, the dynamic range was really only about 500.

The document also provided me with three critiques of my application. One of these reviewers was clearly inexperienced in the language of critiques because he actually praised the work with terms such as "sound thinking", "original approach", and so on. The third reviewer was brief and said that as I had not stated precisely what I intended to do, he was not convinced the experiments would work and suspected the example I provided was wrong.

It is the critique of the second reviewer that needs more critical attention. I had stated that as we are more distant from fish than we are from rodents, comparing fish genes with their human counterparts was better than comparing the human with mouse genes. In other words, the common ancestor of mice and humans is so recent that we cannot assume that similarities between their genomes represent common function. But in the case of fish and humans, there has been sufficient evolutionary time for mutations to destroy the similarities that arise simply out of a common origin. Now, I thought this to be an unalterable fact but I was told that "while possibly true, it would seem that this claim is premature at the moment," from which I can only conclude that the reviewer does not understand that evolution is irreversible.

Actually, it was quite easy to deconstruct the critique, which must have come from a member of the Genome Politburo because he produced that heavy old argument that we will soon have the sequence of both the human and mouse genomes and we don't need any of this fish genome rubbish. He totally missed the point of the research — which was to try to find control sequences —because he thought that I should use cDNAs from mouse or human genes. Anybody could do that.

I have seen guidelines on what such committees should look for in applications suitable for acceptance, and I now offer some convenient guidelines for rejection. If it is novel and nobody knows whether it will work or not, call it "over ambitious and superficial"; if it offers a better way of approaching a problem, protect all established plans by calling it "unnecessary and redundant"; and if you find that the applicant has never done an experiment on the 8th base of tRNA, say he lacks the "necessary experience to conduct these notoriously difficult experiments". And turn it down.

Magazine

False starts

Remembrance of things past… rumination

Sydney Brenner

Last night there was an earthquake a few hundred miles away from where I am writing this in California, but it was strong enough to wake me. For a minute or so I could feel the building flapping and rocking and the furniture shaking and moving around the room. This was followed by a deep silence, but I could not go back to sleep, and there is nothing like lying in bed after an earthquake has failed to get you, for a good rumination. Notice I did not say I lay in bed in the early hours thinking, because it took me years to realise that while I was schooling myself to be a theoretician, becoming a ruminator would be my best shot at it.

Thinking conveys the images of ice and steel and clear, pristine, hardness; whereas ruminating is much more meandering and slushy and not really directed at anything in particular. But because one can mull things over, and turn them upside-down and inside-out, many problems can be solved in this way, often by mistakes, by puns and other misdirections. I have always envied those people who took to mathematics and not only understood it but also knew how to use it. My school mathematics ended with quadratic equations and I spent many hours trying to learn calculus and other branches of mathematical analysis that I thought I would need to become a scientist. But, somehow, it did not become really firmly lodged in my head.

Only the other day, I finally solved a problem that had occupied most of my ruminating time for the past year. It was a simple integration, but the answer I kept on getting was wrong, missing one term which I knew had to be there. I had left something out at one of the steps but I did not know what it was. I could, of course, state the answer, which nobody would query, but that would be like faking an experiment and one might be caught out by a naïve question at a seminar, such as "Where does k2 come from?"

All of this was galling and no amount of analytical thought seemed to help. Then in a sustained bout of rumination, the answer oozed out. I had simply assumed one of the boundary conditions to be zero until I found it was not by running everything backwards, which was not quite correct but reached the right point anyway. I could then write it all down and feel very smug that I had achieved it all by myself and without cheating.

I discovered a long time ago that I was a geometer and that I needed diagrams and pictures to understand things. In the past few months I have been struggling to try to understand stochastic processes. I was doing pretty well with balls in an urn until I came across two things which I am sure are related: eigenvectors and eigenvalues. I have spent endless hours ruminating over these terms but, of course, it is hard to contemplate them without involving my friend Manfred Eigen, and all the more so, because I am sure he would know all about these matters and find my ignorance laughable. I may actually have to go and look them up in a textbook if I continue to make no progress by rumination. But I did sort out what the ergodic theorum is all about, although I could not for the life of me understand the proofs offered in the textbooks, largely because I have not gone anywhere near something called measure theory.

Biology suits ruminators largely because, unlike physics, it has no formal mathematical structure that the thought mechanics can use. In the last fifty years or so of my misspent youth, I have wasted hours trying to master the many attempts to find such a structure. There was Woodger with his Axiomatic Method, replete with all the stuff from Principia Mathematica; Rashevsky (and many others) with heavy partial differential equations; and more recently, René Thom and others, pressing topology on us. I almost forgot chaos and something called the edge of chaos, and fractals, of course.

The wonderful aspect of biology is that one can combine rumination with having a go at the bench, or, as some may prefer to state it, theory and experiment. The art of the biologist is not only finding solutions to puzzles, but finding ways of showing that these are true. Sometimes the way itself takes almost a lifetime to develop, but it is always satisfying to get there in the end, especially if it all started from a vague rumination.

François Jacob likened the evolutionary process to "tinkering" or "*bricolage*". This is a most un-French thought, which Jacques Monod, René Thom and all other righteous Cartesians would find ridiculous, perhaps even contemptible. But as an empiricist from the pre-genomic era, I find it almost exactly right, although not the end of the story. What sort of tinkering can it be? How can it produce non-trivial changes without making a complete mess of everything? Now there is something for you to ruminate about, the next time an earthquake wakes you up in the early hours.

Magazine

False starts

The book of man

Sydney Brenner

From time to time, we need to be reminded that not so long ago information was distributed in the form of words and pictures printed on sheets of paper and bound into what were called journals and books. Although everything is done today in a very different way, the fact that the products of scientific research are still called papers links us to the past. My father once told me that he could remember being taken as a small child by his grandfather to a real library, a building in which vast numbers of books and journals were stored. As everybody knows, almost all printed matter was destroyed in the Great Paper Plague; we know more about ancient Egypt and Sumeria, whose people had the foresight to write on walls.

Now, to commemorate the centennial of the first complete sequence of the human genome, the Institute of Biohistoriography in Shanghai has reproduced a book called *Human Genes* that was published in the early years of this millennium. Apparently, the complete sequence was never printed as, with one kilobase of sequence taking up one page, it would have occupied three million pages. What *Human Genes* contains is just the protein-coding sequences of some 3% of the genome. Comprising 25 volumes — one per chromosome — it is still 100,000 pages, although, by the standards of those times, this was not very large, as there were several journals producing some 20,000 pages of printed material every year.

Human Genes contains additional material in the form of what was called annotation, which includes a translation of the sequences into amino acid sequences. The first gene on chromosome 1, reading from right to left, begins with the sequence (met).val.arg.ala.tyr.ser.his.ile.ser (VRAYSHIS) and the significance of this was first explained in a short paper written by a scientist called L. Orgel[1], which is reprinted in Volume 1. It has to be said that the reproduction of *Human Genes* is a collector's item and not really suited to casual reading.

More widely interesting is the accompanying old-fashioned compact disc, which contains the genome sequence set to music. Towards the end of the twentieth century a minor composer, Susumu Ohno, experimented with the transposition of gene sequences into musical form. When the pieces were performed they were found to resemble the compositions of well known composers. Some genes sounded like Mozart, others like Chopin.

I don't know whether these transpositions were made on a larger scale, but what we have on the compact disc is much more elaborate. It is an eight-hour cantata, set for full orchestra together with several hundred voices, composed by Ragami Nagata, who, like Ohno, was Japanese. The text he used is not the original human genome sequence but a later one which included the polymorphisms, thus allowing an extension of the basic vocabulary of A,G,C,T to include R,Y,N,M,K and so on. He also introduced the letter I for those A sites modified by editing. This greatly increased the range of vocalisation and although I am not fond of this kind of music, which used to be called modern, it lessens the tediousness of the performance.

Nagata also invented a new instrument, called a tryptophone, but all efforts to trace a description of it have failed. The compact disc provides us with an original performance, and although the sound has been reconstructed and improved by modern techniques, it still preserves much of the original quality. You can hear the tryptophone in the 8th movement performing the TGG triplet repeats. Research at the Institute has shown that there were other musical settings of the human genome sequence. Songs, several operas and even a Broadway musical comedy are known but these remain curiosities and have been rarely performed over the past hundred years.

A pioneering attempt to transfer the sequence into odours is also available from the Institute. It comes in the form of a program that has to be run on an old fashioned two-dimensional computer capable of synthesizing the smells. As with Nagata's cantata, variety has been introduced by using the polymorphic sequence. This is not to everybody's taste (or smell) and I, for one, found that I adapted too quickly and the performances quickly became flat and bland.

For those with a more contemporary taste, the Institute is making available the newest set of Micro-Av Crystals. These weigh about 100 micrograms and can store 6×10^{17} bits, or 10^{10} genomes, in quantum superposition states in the three-dimensional lattice. The crystal contains genome sequences of all of the people in the world, which will be kept up-to-date as new people are born. This is truly the human genome sequence complete and a far cry from the early work of *Human Genes*.

[1]He noticed the similarity of this motif to the first word of an early Aramaic book called *Genesis* which, from the four fragments that have survived, appears to have been a treatise on cosmology and evolution.


Loose ends
by Sydney Brenner
2000

Magazine

False starts

All the world's a lab … and last, The Survivor

Dear Willie,

I'm sorry that you haven't heard from me for so long but having made it into the new millennium, I am writing just to let you know that I have survived, more or less in one piece. For a brief moment on December 31st, I wondered whether my neurocomputer prosthesis was Y2K compliant, or its opposite, complaint; but then, I remembered that neuroelectronic circuits had not yet been invented, and that I didn't have to worry about my neurons zeroing out at the stroke of midnight. A different stroke might well accomplish this, but not that particular one.

Well, here we all are wondering what we can accomplish in the next 1000 years and pondering what we failed to do in the last millennium or at least in the last month of it. We've lost any chances of having a last publication in 1999, but we've gained the pleasure of adding the first one of the year 2000 to our CVs. Actually, what you are reading is my first publication of the year 2000. I noticed recently that its predecessors are solemnly listed in Medline but with the note that no abstract is provided. This fits nicely with my view that each of my complete pieces is but an abstract of some greater unwritten work. It also led to my realisation that if you can write an abstract that says everything you want to say, there is no need to produce the full version of the article; why burden the world with massive tomes that nobody will read anyway?

I have been asked by several people how one can become a survivor. Of course, you have to have the right genes and, at the moment, this can only be accomplished by making sure you have chosen the right parents. Many of us come from long lines of survivors and so should have few problems in becoming survivors ourselves. But this is destined not to be the case in the future as medical science ensures that more and more shaky genes remain in circulation.

Having the right genes is a good start towards ensuring one's physical survival, which is essential for everything. But following a few precepts is another, and just as important. Survivors always get asked to say what habits account for their longevity so, before you ask, here are four rules that you need to follow (note how progressive deletion from the right ensures that only the non-redundant information is conserved):

Don't drink cheap red wine with Indian curries.
Don't drink cheap red wine.
Don't drink.
Don't.

Survival in science, and especially in biology, takes something more than having a working body. The most important thing you can do is to stay out of phase. As fashions rise and then fall and then often rise again, it is important to be either half a wavelength in front or half a wavelength behind them. It does not matter which you choose. Although you might think that being ahead is much better, I should point out that it is also much harder; the fashions are almost certain to catch up with you and you will then be smothered. By contrast, staying half a wavelength behind gives you a more peaceful and productive life. You can deal w ith all the problems that the stampeding herds have left unsolved. Of course, in biology, it is often said that once the principle is grasped, the details can be left to others. I have said it myself. But I realise now that some problems cannot be solved without the details; the principle, while true, is vacuous.

Many issues in evolution are going to depend heavily on details, and the exciting part will be how to find them when they are not available directly, as all the contemporary organisms are. Thus, even at the height of the genomic and post-genomic periods of biological research, I still cling to a certain pre-genomic style of science. In fact, if you are working in the backwaters of physiology, you will be several wavelengths behind the current fashion but, I venture to predict, several wavelengths ahead as well. I have seen a number of references to a new science called Physiological Genomics. I thought that a journal with that title was bound to appear in the new millennium, but some research by a knowledgeable colleague has revealed that it already exists.

Continuous visibility leads to survival, or, to put it another way, a sustained impact factor is what you need. How to achieve this is the main preoccupation of most scientists today. They think you do it by publishing in impactful journals, or delivering lectures at prestigious meetings or being asked to speak at important universities. Furthermore, they think you achieve impact by being totally serious. They are wrong. The best way to survive in science, as in other walks of life, is to make people laugh, because laughter registers impact with the greatest efficiency. Risibility is closely related to visibility. This is why Groucho Marx will be remembered long after Karl Marx has been forgotten.

Uncle Syd

Magazine

False starts

Hard cases
Sydney Brenner

Excerpt from the transcript of the trial of T. Cobley *et al. vs* the Editors and Publishers of *Nascence*, before Lord Justice Abel.

Mr R. Gument Q.C.: May it please your Lordship I appear for the plaintiffs, T. Cobley *et al.* in this action.

The facts are straightforward and simply recounted. On or about the 10th of October 2000, the plaintiffs submitted a typescript of a scientific paper to the editors of the journal *Nascence*. Some two weeks later, they received a communication from the editors stating that their paper would be considered for publication and would be sent to reviewers. This was already a major achievement as most of the submissions to this journal are returned unread and some possibly even unopened.

A few weeks later, our clients received a letter from one of the editors, enclosing the comments of three anonymous referees. Two of the referees had only minor comments and asked for a few changes and some additional material. What is important, my Lord, is that both praised the research using words such as "original", "clever" and "novel", as may be seen from the documents in Volume 5, Tabs 23 and 24.

The third referee, Tab 25, was severely critical and claimed that the work was fundamentally flawed and should be rejected. The plaintiffs amended the manuscript and provided the extra information as requested by the first two referees, but pointed out that the third referee had failed to grasp the principle of the method used and that his statements were incorrect. Nevertheless, they had amended the manuscript to emphasise certain of the special features of the work with the express intention of satisfying the third referee's concerns.

The Editor then communicated with the plaintiffs saying that the paper had now been sent for a second deep review, implying, if your Lordship will forgive the jocularity, that the first had been a shallow one. The plaintiffs assumed that this review would be carried out by a new panel of referees but, to their surprise, they discovered six weeks later, when they received a letter from the Editor rejecting the paper, that the second review had been carried out by the original three reviewers.

The Editor in her rejection letter commented that *Nascence* was only able to publish the most exciting and the most revolutionary papers in the field and that the plaintiffs had not succeeded in reaching this standard. The reports of the referees were enclosed. Two expressed satisfaction but the third persisted with and, indeed, enlarged his criticisms (Tab 29). The authors pointed out again that this referee's statements were incorrect, but no reply to their letter was received.

Journals such as *Nascence* have what is called a high 'impact factor', of which they are most proud and which they widely advertise. This factor is computed by counting the number of times papers in their journal are referred to by papers written in later scientific literature. Indeed, this impact factor not only significantly affects the commercial success of the publications but it has come to play an important role in the professional success of the scientists. Thus papers appearing in *Nascence* have a much higher academic rating than papers appearing in the *Patagonian Journal of Knee Surgery*, to give but one example.

The plaintiffs claim that by not being able to publish in *Nascence*, they have suffered injury to their professional careers and are claiming compensatory damages. It can be argued that this is the fate of many scientists and that their claims should be rejected just as their paper was, but we intend to establish that the plaintiffs were wrongfully excluded, that they were unable to confront the negative referee directly and that the Editor was negligent in not checking the validity of this referee's statements. Even though the Editors will claim that many factors were taken into consideration in their rejection, it is a fair implication that it was the negative comments of one referee that turned the balance.

Your Lordship may find it surprising that, in a profession that prides itself on the objectivity and rigour of scientific argument, individuals are allowed to make *ex cathedra* statements without any direct support and that the journals believe that they need to preserve the anonymity of such commentators. Their names have now been provided by the defendants on pain of imprisonment, since your Lordship's ruling that failure to do so would be viewed as contempt of court.

We intend to prove by cross examining the referee that the statements had no justification. We also will show that the Editor, although possessing an academic qualification of some relevance, was essentially a lay person in this specialised field and should have sought additional opinion rather than giving undue weight to a negative view, not once but twice.

We are therefore seeking punitive damages and we hope that this will put a stop to the practice of anonymous referees, so reminiscent of the cloaked accusers in heresy and witchcraft trials of the Middle Ages.

False starts

What lies ahead?

Sydney Brenner

I don't know whether anybody else has noticed the distinct decline in recent years of cases of scientific fraud, plagiarism and other deviations of our noble profession. It seems to me that about a decade ago not a week passed without screaming headlines of faked experiments, cooked results and the lifting of other people's work. I have been thinking about possible reasons for the decline since then, and I hope that this brief summary of my findings will prove useful to other serious students of the psychopathology of everyday science.

The first possibility is that fraud is still going on but the criminals are not being found out. Some of you will remember that a decade or so ago there were whistle-blowers whose mission in life was to bring suspected fraud out into the open so it could be investigated by journal editors, university faculties, NIH committees and even the United States Congress. All of this apparatus seems to have vanished and it is fair to wonder whether the disease is still rampant but is less noticed now that the full time diagnosers have gone. However, I am much more inclined to believe that it is the other way around: the disease has abated, so there is no work for all the watchdogs of scientific integrity. I hastily add that in Washington, at least, there were also political reasons for dismantling some of the apparatus.

If we are agreed that there is less fraud about, why should this be so? I doubt whether, overnight, every faker has seen the light and reformed. Nor do I think that anybody has been deterred by the possible consequences of being caught out, which tend to be pretty boring for the perpetrators and which hurt the innocent more than the guilty.

Could it be that the main motive for people stepping across the line, namely the severe competition in science that young people face, has diminished greatly? It is certainly true that in the last few years budgets for biomedical research have grown, especially in the US, and that pharmaceutical companies have also poured more resources into research. But the number of people in the field has also grown and the competition is much the same. The prizes have also got larger, so I think the reward/risk ratio has remained constant, or nearly so, and this cannot explain matters.

The main reasons for the waning of fraud, I believe, are the increasing technical complexity of scientific research and the change in the modes of communication in science. Gone are the days when one person could set up an experiment, preparing all the components themselves. Then, one could find all sorts of things in extracts of cells and, of course, it was also possible to find things that other people might not find. Today, there are standardised kits for all experiments and fakers will be found out more quickly.

They also must find it much harder to ply their trade given the way that science is communicated now. Any self-respecting faker will clearly want to operate right on the cutting edge of science because otherwise nobody would know about their work. But publication in science has lost the communal basis it previously had. And, as the subjects and as the number of people working in them grow, the journals reporting their work have become so voluminous that nobody can possibly read them. Instead people are turning to searching the electronic publications, which allows them to get what they want without bothering to look at anything else. So it is just that much harder to get your paper noticed, especially as we can trust the referees to reject anything that is unconventional, whether it is authentic or faked. It remains to be seen whether these changed circumstances will result in a class of gentlemen fakers, who have forsaken their egotistical desires and remain content to make up purely conventional and boring papers that will go unnoticed.

There is one other very important reason for the disappearance of scientific fraud. This is the fact that there are now very large organisations doing what is perceived as front line research with very sophisticated equipment. It is almost impossible to fake a structure of a protein, by forging a diffraction photograph. Nobody can claim that they have sequenced the human genome in a garage, because everybody knows you need a factory for that.

If this is right, we can conclude that the old criminals have simply become obsolete, and we are only experiencing the lull before the storm. A new kind of scientific crime will evolve in the next few years, involving those T-shirt criminals, the hackers. They will know how to write programmes not only to create their own results, but also to destroy other people's work. They could also tinker with the literature, inserting non-existent papers of their own and deleting those of their rivals. And they could award themselves grants, promote themselves and, in short, manipulate the world that we are building now. Perhaps the reprint will come to be prized as an authentic document, especially if signed by the author. Or, come to think of it, a hand written manuscript might be the real thing.

Magazine

False starts

The bottom line

Sydney Brenner

In the springtime, young men's thoughts turn to love, but old men begin to contemplate retirement. I have lost count now, but this spring will be either the fourth or fifth time I will have retired and I am now looking forward to the next things I want to do.

When I was in my fifties, twenty years ago, I was worried about retirement, having seen what happened to people I knew when they were tossed out of their places in the world. At that time, I decided that the best thing to do when it came to my turn would be to leave before the execution, don a false beard, and aim to start again by applying for a postdoc position in a new laboratory and in a different subject.

I soon realised that this would be technically quite difficult to arrange. I might be able to change my appearance and disposing of the old body would not be difficult because one could always spread the rumour that one's previous persona had joined a monastery or had become the head of a university. But creating a modest CV and forged letters of reference to cut myself down to postdoc size would not be easy.

In practice, I have found that in any new life you have to start at the top in order to set up a new laboratory and then work hard to get to the bottom to do the things that are really important.

To do this requires careful judgement of how much administrative incompetence needs to be applied to ensure one's descent. As, in this operation, the exercise of power and authority is no longer important, it is best to delegate everything to somebody else and concentrate on getting to the bottom as quickly as possible. I predict that this will become progressively easier as we move into the information revolution and as the new cult of dot.communism progressively gains more converts.

Mind you, the bottom is not what it used to be. I increasingly notice how everything is becoming de-localised so that it will soon be easy to have virtual research institutes, with virtual laboratories, virtual results and virtual publications. Somebody said to me the other day that, in this era, scientists will arrive at the lab and go straight to their PCs where they will read the literature, do their correspondence, plan their experiments, buy their kits, log into virtual meetings, write papers, and carry out all the other activities of important people in important institutions.

What is left out of this plan, I pointed out, is the actual business of doing the experiments. I was told that this would be unnecessary as we could automate everything on a large scale using chips and the like to extract data which, of course, would also be analysed by a computer.

All of this ignores the essential role that is played in science by face to face contact between individuals. I have found that this can quite often spark off new ideas, because when one of the participants gets something wrong the first time it is discussed, this allows the other suddenly to see something new. For this to happen, everybody involved must be at the bottom and reasonably, but not totally, ignorant about the field, while being willing to say what is in their head, ill-formed though it may be. This does not happen in group meetings, seminars or any of the other formalised interactions we have in science.

I have been meeting quite a number of graduate students and post-doctoral fellows in different universities over the last few months. Inevitably, somewhere between the turkey on croissant and the ice cream dessert the conversation turns to the question of whether I have any advice for them. Which fields should they go into? Where will there be new breakthroughs? And what are the best places to go to?

Many years ago I learned how best to give advice to people. It requires a face to face conversation and all I have to do is listen carefully and see if I can discover what it is my client really wants to do. Then I advise him or her to do just that. In this way, I have quite a good record of giving advice.

This can't be done in a group meeting, because nothing general can be said that isn't at the same time completely vacuous. So if faced with a group, after a few platitudes (and plongitudes) I advise those present to take absolutely no notice of my advice. And when they ask me about my scientific successes, I assure them that these depended on my not taking advice from anybody, and especially not from people experienced in the subject.

A reader recently complained to me that my columns were becoming too serious. This suggests that I am rising to the top of the column-writing business and that retirement will soon be necessary. Clearly, I need to give urgent consideration to how to get to the bottom again. The last time I did so was when this column changed its name from *Loose ends* to *False starts* upon moving from the end to the front of the journal; so perhaps I should now become a centrefold and the column could be called *Middle page*.

Magazine

False starts

A natural selection

Sydney Brenner

R.A. Fisher, in his 1929 book *The Genetical Theory of Natural Selection*, noted that Charles Darwin believed in the theory of blending inheritance, and that this conditioned his views on variation and therefore on theories for the possible causes of evolution. Darwin realized that blending, or fusion, inheritance reduces variation and that all variability must be continually at work, or else natural selection would have nothing to act upon. Thus, blending inheritance forced Darwin and others to attach great importance to hypothetical means of producing variability or, as we would see it now, there was a need for mutations to be arising all of the time, to defeat the inevitable regression to homogeneity.

Darwin and his contemporaries were all Lamarckians. The arch-Lamarckian was, of course, Lamarck himself, who thought it was enough for animals to want to change and that the right mutations would be produced to satisfy these desires in their progeny. Darwin thought it was the adaptive changes themselves that triggered the mutations; others postulated evolutionary forces that acted from the outside, or intrinsic urges in organisms themselves.

It was Mendel's discoveries that dispelled all of this nonsense. Most people remember him for his laws of segregation, but it is his theory of particulate inheritance that provided the fundamental basis for evolution by natural selection, and that enabled natural selection to be studied, not as the junior partner in Darwin's theory, but as the central agency working with particulate inheritance. As everybody knows, Mendel's discoveries lay neglected and unknown until their rediscovery 100 years ago this year.

I have gone into all of this because I become more and more conscious that most people do not understand evolution by natural selection. As direct evidence, I offer the following. A few months ago, an old friend, Jack Dunitz, reminded me that in 1994 I had signed a circular letter to do with journal publication, following which he had written to me under a pseudonym and that I still owed him a reply. I have no memory either of the circular or of receiving his letter. However, he was good enough to forward me a copy of his letter, and I reproduce it here together with my belated reply.

Elysian Fields
Box 21
Evolution Department

December 8, 1994

Dear Dr Brenner,

A circular letter signed by you and sent to several colleagues has recently been forwarded to me at the above address. You suggest a system in which editors go out of their way to select the best articles and papers for publication has some features in common with the theory of natural selection that I promulgated in the middle of the last century.

I consider it my duty to inform you that such a system is totally contrary to the kind of selection process that I had in mind. In fact, you are appealing to the intervention of a higher being to select what is good and to reject what is bad. This is not at all what I had in mind.

I regret very much that I did not make myself clearer and that you have misunderstood me in this important point.

Yours faithfully,
Charles Darwin

The Ashes
Inferno Way, Fireproof Box 666
Hell

May 18, 2000

Dear Charlie,

I hope you get this reply which I have had printed on titanium sheets. I trust you recall that your theory included something that was outside organisms and which acted on them to exercise selection. This is the environment.

In our circular, we simply suggested that editors should constitute an effective environment. Perhaps we did not make it clear enough, but it is reproductive success that is important. We were not interested in the papers — these constitute the phenotype; it is the survival of authors that is the key issue. Selection against certain papers would render their authors extinct; they would fail to get grants and gain promotion, and they would not train others. I suppose that with your dependence on blending inheritance and your failure to keep up with modern literature your complaint might be excused.

You will note from my address that I have nothing to do with Supreme Beings. The same could not be said of you.

Yours,
Uncle Syd

Magazine

False starts

Hard cases (contd)

Sydney Brenner

Your chronicler has had several responses to the matters raised in 'Hard cases', an excerpt of the court transcript reported earlier (*Curr Biol* 2000, 10:R127). All who were authors of papers have quoted virtually identical experiences: the rejection of a paper turning on differences between a referee and the authors and always decided in favour of the referee by the editors. They greeted with relish the idea that a referee could be compelled to reveal himself in a court for cross-examination. Others, however, including two editors, felt that the anonymity of referees was sacrosanct and were horrified by the proposition that it should be breached. Readers may be interested to read this excerpt from a case brought before the Court of Appeal.

Mr R.E. Buttal Q.C.: May it please your Lordship, I appear for the appellants in this case. We are appealing against the order of a lower court, compelling my clients to reveal the name of a referee used by my clients in the prosecution of their work as editors and publishers of a scientific journal. M'lud, the function of referees is to provide the editors of such journals with expert opinion on the content of scientific papers, which are often highly technical and on the frontier of advancing knowledge. They are needed to bring a specialist's view to such questions as whether or not the conclusions reached are justified by the experiments or observations reported; whether the experiments were properly selected and well carried out; and, in papers of a more theoretical nature, whether the reasoning used is correct or not. They may also comment on how the authors have dealt with other work in the field.

It is important for the journal, indeed, for science itself, that referees can express their views freely and without regard to any external factors. More often than not, a referee will be junior to the senior author of a paper and if his name were known he might temper his opinions, fearful of consequences to his professional career as an act of retaliation by a powerful figure in his field. Thus, his anonymity guarantees complete objectivity, allowing him to voice his opinions, without fear or favour. In addition, this practice not only ensures that the edifice of scientific knowledge is soundly constructed but it also allows all to use publication in refereed journals as a measure of scientific competence. Breaking the anonymity of referees could ultimately lead to the destruction of the whole peer review system in science and place everything in the hands of the powerful few. Although it has been put to your Lordships that this is a solitary instance, we are concerned that it might become a precedent and we therefore ask the Court to grant the appeal.

Mr R. Gument Q.C.: We do not disagree with the appellant's argument that the anonymity of referees guarantees their objectivity but point out that this is only a halfway measure. There is a good argument for instituting an anonymous authorship of papers, and, although practical matters may stand in the way of implementation, there is no doubt it would double the objectivity of referees who would not know whether they were trouncing a junior colleague or insulting a senior scientist.

This is not our main point, however, because our case was directed not against the referees but against editors. We agree that editors require expert advice to make the decisions that only they can make. This is especially true for those journals which cover an exceedingly wide range of scientific topics with editors who are not experts in one field, let alone the whole range. They need to be reminded that they must act carefully and fairly in dealing with the referees' reports, which are to them and not to the authors.

Evidence was given in the lower court by a past editor of a journal who recalled that his practice in the middle of the last century was to quote only relevant excerpts from the referees' opinions supporting *his* case for accepting or rejecting the paper. The referees were thus completely anonymous, because the authors were prevented from deducing anything about their identity from their style or the typewriter used. Because of the growth of the scientific enterprise and the concomitant increase in editorial activity, this practice stopped and editors now simply transmit the referees' reports to the author. Occasionally, they point to a statement which requires the author's attention. Often the reports are contradictory, and they also contain gratuitous comments on whether the work is suited to current fashions of science and the journal, which have little to do with the objective review of the science itself.

We had asked the court to order the referee to appear and defend the statements made in his report, which we thought were incorrect, and which we claimed were inappropriately relied upon by the editors. Our argument is with editors not with referees; we only ask that they take all measures possible in their evaluations; they should not be allowed to hide behind the anonymity of referees, and not take responsibility for their actions.

The court adjourned at 5.00pm.

Magazine

False starts

Unconscious secrets

Sydney Brenner

I am sometimes asked where I find the material that goes into these columns and whether it is difficult to write something new every month. When I started it was easy because I had a large stock of material accumulated over many years during which I did not write columns. And, yes it is becoming increasingly difficult as the stock has dwindled with the passage of time.

I am always on the lookout for anything ludicrous and bizarre in science but there isn't much more that I can add to the absurdities of scientific publication, grant-giving bodies and the human genome project. Evolution remains a good topic and I am coming to believe that consciousness is another.

I am told that consciousness is the most significant problem we can tackle in biology and solving it will be the landmark of the 21st century, as DNA was in the last century and natural selection in the one before. If these are any precedent, we shall have to wait fifty years for a solution, although this will be too late for most readers.

You may recall that I have written on this subject before, but it seems that nobody took much notice of what I had to say as I have never seen it quoted, except in jest. I shall therefore have to start at the beginning and, for starters, let me point out that consciousness is a field in which philosophers are very active and not in full retreat as they are in other areas of biology. Since consciousness is connected with the soul, many other people are actively involved, most of whom will not be found in any department of neurobiology. Also these people write a lot and apparently don't have to do any experiments or satisfy referees — much like me, in fact.

The first thing for a novice entering the field to beware of is that consciouness has quite a lot to do with language, and especially with the use of language by the practitioners themselves. Thus you will find that awareness of the self easily becomes self-awareness, that awareness is about attention and that attention is a brain activity that can be measured and studied. Notice also that consciousness of the self is different from being self-conscious, which has connotations of awkwardness and embarrassment.

You will find that there are those who think that consciousness is simply going to be more of the same thing. That is, it will be explained in terms of the same machinery of brain function by which we explain other functions, such as visual perception, in terms of neurons, synapses and circuits. Other people think this will be insufficient and that we will need to involve new scientific principles and perhaps even new physics.

However, before everybody rushes off to learn quantum mechanics or to read Gödel, just think about the following. I know quite a lot about my conscious self, as you do about yours. I do this with something called thinking. Thought is central to my consciousness, so we want to know how we think. Thought is generated from within our brains, so generation of neuronal activity from within the head seems important. Of course, we might be able to think about thought and think new things at that. All of this is important not only to myself as a human being but especially to myself as scientist, because what I find absolutely remarkable is how much we can find out about brain activities that we cannot contact directly. Science has revealed for us what goes on during every picosecond in the molecules in our photoreceptor cells, every microsecond in the subsequent molecular events in those cells, and every millisecond in the neural circuits that connect these cells to others. Science has told us about unconsciousness, about phenomena outside the scales of space and time that govern the formation of our own selves.

If we were conscious of these molecular fluxes within out brains, the tops of our heads would be blown off, so it is a good thing that the unconscious activity of the brain needs science to tell us about it. It is still the most important function we should be studying, because everything we learn about neurons and their circuits will find its place in our understanding of the brain. When we discover the neuronal basis for generating activity within the brain, and how this may 'playback' experience, we will have started to learn about thought. And at that stage I suspect that consciousness as a problem will simply disappear and won't require a solution in the form that is being posed today.

Years ago, students frequently used to ask me what will be the big breakthrough in neurobiology. I could tell them that it had already happened and that they were more than a half a century late. It was called the neuron hypothesis. Today it is more than a hypothesis, it is a fact. It did for the brain what the earlier cell theory did for the body: it told us that the organs of the body were collections of cells that, by division of labour, performed the physiological function ascribed to them. Perhaps that is the best way to look at the brain — as an organ, a hybrid of an endocrine gland and a kidney, with the dual function of secreting thoughts and excreting words.

Magazine

False starts

Empty chateaux

Sydney Brenner

When I woke up on the morning of Tuesday 27th June 2000, I noticed no change at all. I telephoned a few friends and they confirmed that their lives were not much different that morning. One said he had a slight hangover but he could account for this minor deviation. For years we had been told that once we had the sequence of the human genome, everything would change. So how come after the rough draft of the sequence was announced in a grand ceremony at the White House, neither I nor my friends experienced any of the predicted effects. Was it the roughness of the draft, I wonder, or does the magic still lie concealed in the 5–15% of the genome that is either un-sequenced or unassembled?

Although there are many candidates contending for credit for the sequence, it seems that the Almighty got a fair share of it that Monday. One of the leaders of the Western world was quoted as saying that we had uncovered the script that God used to create human life, thus reducing the human achievement to a modest piece of celestial gene hacking. Some commentators stated that we had now "deciphered" the human code, an exaggeration that may well survive unbeaten this millennium. And, of course, there was a great deal of discussion on whether this was the beginning of the end, or the end of the beginning, or somewhere in the middle of the beginning of the beginning.

We know we are nowhere near the end because of the still great uncertainty in the number of genes in the human genome. Three recent papers, which got the popular press steamed up, each gave different estimates, ranging from about 25,000 to more than 120,000. People get quite shaken by these wild fluctuations and they really want to know whether they are only twice as complicated as a fly or as a worm, or whether they can seek comfort in the larger number. My bet is that it will be close to 50,000. I would prefer to call these genetic loci rather than genes; it will take some time to find out how many different functional products these loci have.

After every party some people always stay behind to clear up the mess and put everything away. The captains and the kings have departed, the shouting has died down and hyperventerlation has ceased. We can walk around the deserted chateau and look at the ancestral portraits on the wall. In Chateau Genome we would find evidence to refute the impression given by the press that the sequencing was carried out by two people starting from scratch, with a little bit of help from Jim Watson.

The first person to set up a large sequence project was Akiyoshi Wada, who, in the 1980s, tried to initiate large-scale sequencing using the original Sanger radioactive methods. He had three industrial partners: one to automate the sequencing reactions, another to prepare preformed gels, and a third to undertake scanning of the autoradiograms. He correctly predicted that a factory approach to sequencing would find a ready market. His project was ahead of its time and although some tens of kilobases were sequenced using his system, it failed because the right technology was not yet available.

Fluorescent primer sequencing, introduced by Lee Hood and Lloyd Smith, the invention of chain-terminating reporters by George Trainor at du Pont, and the development of sequencing machines by Applied Biosystems were essential steps in making large-scale sequencing possible. So, too, was the availability of the relatively cheap large-scale computing to handle all the data. To plagiarise Groucho Marx, it was technology and money, and computing and money, and management and money, and cash and money.

In the early days of discussions of sequence factories, as first put forward by Walter Gilbert, most people found the whole idea of a sequence sweatshop distasteful and demeaning but few people came up with alternatives. I had a very good scheme but like most of my other proposals in genomics, nobody took it seriously. I thought we should put sequencing machines into shopping malls and supermarkets and let people pay a couple of dollars a base to run them. Each day a 'bingo' sequence would be displayed above the machine. Anybody finding this in the sequence their dollars had paid for would receive a prize of $1,000. The profits from the enterprise would be used to pay the exorbitant salaries of bioinformaticians required to develop algorithms to select the sequences and to make sure that we would not be ruined by picking an *Alu* or some other highly repetitive element as the bingo sequence.

I was once asked whose genome would we first sequence. My reply was that it would be the Unknown Genome. But it occurs to me after the recent events that we need to recognise symbolically the large number of people who made the draft sequence possible. We need to have the Tomb of the Unknown Sequencer and on every anniversary of what might come to be called Armistice Monday, we should pay our respect to these unsung heroes of the Human Genome.

Magazine

False starts

Inverse genetics
Sydney Brenner

The concept of reversed — or, as I prefer to call it, reverse — genetics was first formulated by Charles Weissmann in 1978 (*Trends Biochem Sci* 1978, **3**:N109). In this form of genetics, a nucleic acid was modified at a predetermined position *in vitro*, and the phenotypic effects of this mutation were then assayed either *in vitro* or *in vivo*. In contrast, the classical form of genetics relies on first finding a mutation by screening for phenotypic changes and then identifying the gene carrying the mutation. In other words, forward genetics goes from phenotype to genotype, while reverse genetics goes the other way, from genotype to phenotype.

Charles Weissmann was the first practitioner of reverse genetics, implementing site-directed mutagenesis with the genome of Qβ, a small RNA phage (*J Mol Biol* 1974, **89**:255). Mutations in the phage were made by incorporating modified bases at selected positions during *in vitro* synthesis of minus strands. The plus strands were copied *in vitro* and then either studied directly or introduced into spheroplasts, and the resulting mutant phages were recovered for further studies.

All of this took place in the years BC (Before Cloning) and when these and related ideas were discussed at a meeting in 1978 in the early AD (After DNA) days, most of the promise of the new DNA technology was still a dream. Interested readers, and certainly historians of the modern era of molecular biology, might consult the book reporting that meeting (Human Genetics: Possibilities and Realities, Ciba Foundation Symposium 66, *Excerpta Medica*, 1979) if only to savour how the dreams of 20 years ago have all become part of everyday practice. That is why, with the exception of a few diehard geneticists, most people now believe that reverse genetics is the normal way of going about discovering the functions of genes. Creating transgenic mice by knocking out specific genes is a classical (if one may use the term) example of the application of reverse genetics.

Some time ago, I began to use the term inverse genetics to explain to audiences how we may use information recovered from different genomes to inform ourselves on function. In particular, I wanted to show how we can use time to help us in this quest. In both forward and reverse genetics singular changes made in one gene are assayed for phenotypic effects. Thus we study and compare two genomes, the wild type and the mutation, looking at a few differences embedded in a vast sea of constancy. In inverse genetics, we do the opposite, we look at what is conserved, that is kept constant, in a vast sea of randomness.

The best way to understand this, is to imagine that we have two human (or mouse) lineages that separated from each other at some time in the past, never to exchange genetic material again. The further back the separation, the greater the extent to which nature would have randomized inessential sequences by mutation. It is necessary to go back as far as possible or else the constancy we will be looking for will be masked by that of common origin; what we are looking for is the preservation of those parts of the sequence required for the phenotype common to both lineages.

Unfortunately, the two lineages are not available in the form discussed above, but we do have a good approximation to it. The lineages of teleost fish and mammals separated about 500 million years ago, and although fish and people do not look the same, they have many common physiological systems and anatomical features. Thus, for these phenotypes the methods of inverse genetics will be directly applicable. In addition, we can move segments of the genomes between the two lineages and this enables us to test whether fish genes work correctly in mice, that is, whether they give the same phenotype as the corresponding mouse genes.

Older readers will recognise that this experiment is like a cross between fish and mice and, indeed, in the limit we could study recombinants in which the fish gene has been substituted for the mouse gene. Inverse genetics may also allow us to discover what changes have taken place in the genomes to account for the differences between the two lineages. Note that as in forward and reverse genetics, we do experiments on genomes, with the difference being that, in the case of inverse genetics, evolution and time have done most of the work for us. We already have extremely long-term support for our research.

Some of my readers may be surprised by the seriousness of this piece. For them I point out that there may be a third form of genetics, perhaps called perverse genetics in which everything is done by sequencing and computers, without any recourse to biology. I remember that years ago, when people were searching for good models to study developmental biology, I classified animals into three classes: vertebrates, invertebrates and pervertebrates; the latter included unlikely metazoans, such as slime moulds.

Magazine

False starts

Book-keeping

Sydney Brenner

Books are my greatest weakness and collecting them and other printed material is something I have done all of my life. I still spend several hours a week wandering around in bookshops, and the reason I'm late for appointments in Cambridge is that I have a flat above a bookseller with a large stock of remaindered and second-hand books.

My passion for the printed word began soon after I learnt to read and the first of my purchases was a second-hand comic book bought for one penny. Serious contact with books came later when I joined the Carnegie Public Library in Germiston, near Johannesburg, and especially when, after the age of 11, I was allowed to read and borrow from the adult section. I used to visit my uncle's shop in Fordsburg and found a nearby shop that sold second-hand copies of American science fiction magazines. I began collecting *Amazing Stories* and later followed this with science fiction paperbacks. Like many of my other books from this period, their pages are now yellow. Of course, all the wonder of these books was ruined once NASA finally reached the moon.

The modern generation reads and buys books on a computer screen. I tried the latter once to find an out-of-print book, but never again. I was not allowed to browse and kept on getting demands for the details of my credit card. By browsing, I mean wandering around from shelf to shelf, picking out a book and reading some of the pages. Even if a dotcom allowed me do this, I would still feel unsatisfied because being physically in a bookshop and actually handling books is an essential part of the pleasurable activity.

A visitor once asked me whether I had read all of the books I have on my shelves. I confessed I had only read most of them, not all, but that some I had read more than once to make up the average. Those that remain unread have been acquired through either insufficient browsing or seduction by a bargain price. I intend to read these books in my next retirement, when I promise myself and others that I will get all of my letters and papers in order, sort my books and dispose of those that I should, but can't bear to, get rid of.

I have acquired some of my books in an interesting way. In 1979, when I was in hospital and later at home recovering from the aftermath, I suffered from insomnia. To fill the time, I spent hours listening to the radio. In between listening to a live commentary of the attempted coup in Spain, I heard a series of talks, entitled *Promenades*, by a historian of France, Richard Cobb. I found his views of provincial France fascinating and as soon as I could get to a bookshop I bought the printed version of his talks as well as several other books by him. However, I decided that I would leave one of the books, *A Second Identity*, for a later purchase.

This was a mistake and one that I, as a veteran book browser, should have been the first to recognise. The rule is: always buy the book when you see it, because there will be another book-hunter who will get it if you don't. When I returned some time later to get it, the book was no longer there. I tried ordering it but discovered that it was out of print and unobtainable. So I had to settle for borrowing it from the Cambridge Public Library. Soon after this, I was asked to review a proposal for a book on molecular biology by Oxford University Press. As they were the publishers of *A Second Identity*, I said I would review the proposal in return for a copy. They ransacked their warehouses, but not one copy could be found.

For the next 18 years I visited every second-hand book shop with the fantasy that somewhere, someone owned a copy and extreme circumstances, even death, would have forced its sale. I haunted market stalls in remote East Anglian towns, and second-hand bookshops in America, France, Germany, Norway, South Africa and Canada. I even dropped into one in Dar es Salaam. I did find several books this way, even some by Richard Cobb, but not *A Second Identity*.

Periodically, I would borrow it from the Cambridge Public Library and reread it and, over the years, I began to entertain the thought of stealing it, or to put it more accurately, taking it out on a permanent loan. My plan was to borrow the book and then report that I had lost it in some irretrievable way, such as by its falling out of a window of an aeroplane, or being eaten by a hyena in East Africa or plucked out of my hand in a typhoon in Japan. But I never did so, not because of any moral qualms, but simply because I could not find a convincing story that would not immediately arouse suspicion.

In 1998, I was discussing several matters with a historian of modern biology and told her the story. "Oh", she said, "you should ask my husband to get you a copy, he is a dealer in rare books". I immediately got in touch with him and a few months later I was the proud owner of a legally acquired copy. In 1999 he wrote to me and said that he had another copy, which he knew would excite my special interest as he had bought it from the Cambridge Public Library at a sale of their surplus books. I now have that one as well.

Magazine

False starts

Umberto echo

Sydney Brenner

When I began writing these columns I had no idea how they might develop. I had accepted the invitation thinking that I would have time on my hands that I could devote to the written word. Part of my intention was to produce pithy, well-chosen comments on contemporary biological research, and to use the opportunity to say all the things one wants to say, but that are excluded from papers by referees and editors on the grounds that they are speculative and unsupported by evidence.

As it happens, I did produce a few semi-serious columns, but luckily my better half took over and I became more interested in the comic aspects of what we do. Parody has always attracted me, and as a student I produced scripts or, more accurately, scribbled notes, for cabaret acts at lab parties. There was a re-enactment of the rediscovery of Mendel's laws to be performed as simultaneous monologues in heavy German accents by three actors disguised as Tschermak, Correns and de Vries. There was the Lives of the Great Composers series, one of which featured Berlioz sitting in a morgue holding the hand of a corpse and singing: "Your tiny hand is frozen…Mmm! I must tell that to my friend Puccini." There were lectures on schizophrenic acid and related phrenane derivatives and a transformation into science of *Les Enfants du Parodies*.

I have enjoyed finding rare examples of problems that by their absurdity allow one to find the truth, and I like the resolution that can be generated from two contradictory cases. My columns on the reconstruction of the present by some future historian's interpretation of surviving fragments involve a careful selection of the fragments to make the spurious theories proposed appear very likely. They are also allegories of how we can go wrong in research when not all the facts are available.

After a few years of writing my monthly pieces, I began to consider myself a man of literary talents, especially when I found that my scientific work was fast being forgotten and I was achieving more fame as a writer. I was in danger of becoming over-impressed by my literary inventions when I was brought to a halt by my discovery that it had all been done before by Umberto Eco in a series of columns he wrote in 1959–1961 for an Italian literary journal. These were translated into English in 1993/1994 as *Misreadings* and *How to Travel with a Salmon*, although they only recently came to my attention.

Umberto Eco is a Professor of semiotics and, notwithstanding the title of one of these books, has very little to say on molecular biology and genetics. I am not sure what semiotics is — it sounds like half an ear to me — but Eco is clearly a literary man, a novelist and a writer on many interesting subjects. I am therefore extremely worried that some future doctoral student in the field of History of Ideas will draw the conclusion from textual comparisons that much of what I have written derives from Eco.

Before I hear mutterings of 'plagiarism', let me assure my faithful readers that I totally deny that charge. But I have to agree that an explanation is required to account for the homologies in the two oeuvres and to explain why Eco's pastiches of the future, may lead people to conclude that there is some connection between him and Uncle Syd. Fortunately I have been able to discover an elegant theory which explains all and which accords well with the neo-avant-garde aspects of post-modern thought in both science and the humanities.

The more educated of my readers will know that two different geometries were generated by modifying the axiom of parallel lines in Euclidean geometry. I propose to do the same for the central axiom of causality in one particular set of dimensions. This axiom states that if event p causes event q, p must precede q in time. We will allow that even if p follows q in time it can still cause q. "Nonsense", I hear you say. But consider the following: suppose ideas exist in a different dimension from the real world and have their own history and temporal evolution, and suppose they are signalled in the real world only through agents such as Aristotle, Jesus Christ, Karl Marx, Umberto Eco and Uncle Syd. There is no reason to believe that the mapping of the sampling process need to be conserved in the time co-ordinates for the two worlds.

It therefore makes sense to consider such questions as the influence of Marxist thought on Christian teaching. In the dimension of ideas this could well have been the correct causal relation; the fact that the two samplings have an opposite sign in our time dimension is neither here nor there.

This opens up an entirely new approach to studies in the history of ideas, placing the emphasis on the ideas and not on the human agents that sampled them. I am of course sure that Umberto Eco's writings were independent of my own, but his ideas could have been influenced by mine. I can now safely leave the deeper connections between his writings and those of Uncle Syd to a PhD thesis.

Magazine

False starts

Tale fin

Sydney Brenner

A few readers of my last two columns may have suspected that something was afoot. Why, they might ask, does he suddenly produce not one, but two confessions? After shamefacedly exposing his tendency to consider book theft as a way of acquiring knowledge and trying to reverse the hint of plagiarism in his works by suggesting that it was the other way around, we might expect anything.

Well, the explanation is quite simple. I wanted to set the record straight, to tidy up all of the loose ends and to have no more false starts. After seven years of labour in the field, 84 columns, I go on to a well-deserved rest. I find it hard to believe, but there must be some graduate students who began reading me when they started research and who have got their PhDs by now.

I considered signing off with a farewell letter from Uncle Syd to Willy, but I realised that Willy, who had lived in an accelerated universe, must by now be too old and doddering to need advice. As for Uncle Syd, even he could not find enough momentary clearings in his Alzheimerian haze to give any.

Somebody — I think it was John Maddox — once called me the *enfant terrible* of molecular biology, but that image could not last forever and I was rather pleased that I was able to replace it with Uncle Syd, that wise and wily old bird. I do like the way he spoke with complete authority on matters he knew very little about and I find his emphasis on form rather than exact content a most congenial way to view the world. Uncle Syd could always be relied upon to provide the advice that everybody wants to have and to discover spurious and convincing reasons for avoiding doing all the things he was supposed to do. He knew all the ropes and especially the nooses that can be used to hang someone.

Before we take leave of him, I thought you might be interested to hear his pre-Alzheimer views of data-mining, an activity that seems to be gripping everybody's attention. Apparently, he'd gathered, there is so much to glean from existing data that those miners who miss the gold rush can still find a few grains, and even some nuggets, by re-sieving the tailings. This is done by sending software agents to the databases to perform the dirty work, while their masters luxuriate near the pool.

Uncle Syd also observed these scavengers hovering around the public databases and the organisations that put data into the public domain, and getting the gold, so to speak, before the race had been run. Some agents, he noticed, convert their findings into cheap trinkets that can be sold to the natives, who are not familiar with the data miners sophisticated approach to science and life. So widespread has data-mining become that Uncle Syd produced a definition of it: what's my data is mine and what's your data is also mine.

Over the years, I have lamented the disappearance of both thought and experiment from biology and the rise of 'e-biology'. Something tells me, however, that we will soon see the return of older, better ways. Of course they will be practised in secret to begin with, and some practitioners may be martyred for preaching heresy. But gradually, I predict, these pioneers will come to be recognised and followed. No longer will the man carrying an ice bucket through the corridor in a particular way be keeping his dry martinis cold while he reads his e-mail, or hastens to attend his e-meeting or to send his e-report to his e-voice-mail. If there are people out there who are doing experiments or thinking about their results, let's get in touch; just write a letter, or if you are nearby, drop in, but do not on any account send an e-mail.

When one stops doing a job, one should immediately go and look for another one, if only to provide an excuse for not doing all the mundane things one has promised to attend to after retirement. The weightier the job, the better, to give substance to the sentence beginning 'Heavy pressure of work…'.

I am now concerned not only with what I am going to do next, but with how the journal will replace me. Before readers rush to cancel their subscriptions, they should listen to a suggestion that I am sure the editor will heed. The journal should institute a Personal Services column in which scientists could place ads such as one sees in the literary magazines. For example:

Honest, genomic scientist, male (XYY), tall (5'1") slim (206lbs), youngish (56), interested in bioassays, high-throughput sequencing and brain surgery, seeks attractive, mature (20), cultured (37°C) microbial geneticist of either, both or no sex, with a view to collaborative grant requests and co-authorship of papers.

And here is mine:

Elderly, white, male, column writer, seven years experience, self-employed scientist, explorer, adventurer, inventor and entrepreneur seeks young, naïve, preferably female editor of newly formed scientific journal with a view to obtaining unrefereed access to as wide an audience as possible. Has good title for a column: 'The Well-deserved Rest.' Please write, quoting circulation and impact factor.