Journal of Chromatography, 468 (1989) 35–42
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROMSYMP. 1540

CHROMATOGRAPHY AND THE DISCOVERY PROCESS

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SUMMARY

Though each science has its own special features, chromatography neatly and simply illustrates most of the significant characteristics of the discovery process. These include multiple discovery (and its logical counterpart "adumbrationism"), missed discoveries, the dominance of a problem, the crucial role of observation, the advantages of tangential approach, analogy, and serendipity. The story of chromatography also brings out the contributions of the craft and scholarly traditions, the influence of human interactions, and the impact of the intellectual climate. The paper gives examples of these various factors, and stressed the importance to science of collecting information now on how discoveries are actually made, particularly for those discoveries which may not seem to be paradigmatic.

From the mists of chromatographic time, two strong figures emerge, the later more clearly than the earlier.

Michael Tswett (1872–1919) (his surname is the Russian word for colour, especially the colour of plants) died largely unrecognised in Voronezh. Opinions vary as to the essence of his discovery, although his work was fundamental for chlorophyll chemistry and he gave a very clear account of the processes we now understand as chromatography. There were many [such as Schoenbein (1861), Goppelsröder (1861 and later), Day (1897, although he appears to have been overrated in a good deal of the literature), Engler and Albrecht (1901)], who had published related work of which Tswett appears to have been well aware. Indeed Tswett makes mention of Goppelsröder in his classic paper[1]. (For a particularly clear and detailed account of the early history of chromatography, see ref. 2). Further, Bayer[3] has shown that the basic principles of gas chromatography were put forward and demonstrated practically as early as 1512; Tswett is probably remembered chiefly because his real interest lay in plant pigments, and it was Edgar Lederer's work on carotenes in the 1930s that effectively resuscitated his method. Previously it had been condemned by Willstätter and Stohl (1913) because they had been unsuccessful in the preparative purification of chlorophylls using "Tswett columns"; apparently they had failed to notice what Tswett had already made clear, namely that chlorophylls are destroyed by "aggressive" adsorbents and therefore required materials such as powdered sucrose or inuline (see ref. 4). Finally one must recognise that Tswett's proposals were against the current of the time, where synthesis, isolation and purification were the philosophical essentials of organic chemistry, while Willstätter, with his traditional techniques, was

0021-9673/89/$03.50

the great figure in the subject. It is perhaps worthy of comment that organic chemists today are still relatively uninterested in isolating all the components either of natural material or of experimental reactions.

Archer Martin (born in 1910) (whose name in English refers to a clever and remarkably consistent bird –there were twelve pairs of martins at Selbourne two hundred years ago in the time of Gilbert White and I am reliably informed by my ornithological colleagues that there are twelve pairs in the parish today) invented partition chromatography with Synge in 1941[5], paper chromatography with Consden and Gordon in 1944[6], and gas–liquid chromatography (which had been "predicted" in the 1941 partition paper) with James in 1951[7] (and which was then rapidly taken up and developed by ICI, BP and Shell among others). As is common in the history of discovery there were others who were working on related lines, and who would probably have got there in time if Martin had not got there first. Hesse, Cremer, Claesson, Glueckauf and even myself were all working on gas chromatography before Martin, but we did not see the essential step (to use partition rather than adsorption columns). And then there is Bayer's chap. But we must avoid the pitfalls of precursoritism or what Merton[8] has called "adumbrationism", the attempt to discover some earlier historic event which might have changed the development of science, but for some reason or other did no so. It is all too easy to see depth in mere darkness.

Martin has always claimed that his success with partition chromatography arose in part because he and Synge were faced with a real problem, the separation of amino acids, while the crucial step from a clumsy counter-current apparatus was the realisation that it was not essential to move *both* liquids. He and James shifted to gas chromatography after some unsuccessful attempts to automate fractional crystallisation largely, so we are told, because Martin was certain it would work and something surefire might be needed to boost James's morale. I recall once, in the early days, being shown round an industrial plant with Martin. Our hosts were cock-a-hoop about a gas chromatographic analysis that they had taken many months to develop. They would show it to Martin on condition that he kept it a secret. Keeping scientific secrets is not Martins's style, so he suggested that he would at once outline how he would have done the job, and that if their system was essentially different then he would prefer not to see it. It was not.

One curious feature that has distinguished chromatography from other scientific techniques is that it has not for the most part depended upon previous technical developments in other fields, as for example the wartime developments in radar without which modern NMR would have been impossible and radioastronomy would have been hamstrung. (On the other hand, there is little doubt that it benefitted from a change in scientific climate or philosophy). A possible exception is the construction of high-sensitivity detectors, the need for which was clearly recognised by Martin ("I want something much more sensitive; we shall need detection of fractions of a microgram"), and which were crucial to high-performance gas chromatography. But the history of chromatography has been replete with multiple or independent discoveries. I will mention two that are personally well known to me. Several people had thought of developing capillary columns, but the most significant step was taken by Marcel Golay. He was, as I was, a consultant to Perkin-Elmer, and had been asked to turn his mind from the exotica of communication theory to the practicalities of gas chromatography. The latter as it then existed was however too much of a craft, and he demanded that he should work on the theoretically simpler system of an open rather than a packed tube. He then developed a theory of chromatography entirely from scratch. He showed it to me. The first half was quite familiar and had already been independently published by others; the second was essentially new. Perhaps there is a moral here about the dangers of overindulgence in the literature, although my own experience in chromatography would suggest that the reverse is the more common error: I have more than once encountered the view that something had not been done because it was not published in *Analytical Chemistry*. Golay also found it hard to realise that his open-tubular columns could have any application. I thought I was the first one to convince him that they did, but he still went on to drop a clanger about their impracticability at Amsterdam. This is confirmed by Dijkstra[9] who had also been working on capillary columns, but who had failed to do the calculations that Golay had done and was therefore working with gas flowrates that were much too large for high efficiency. My second example is concerned with temperature programming. I was the first to publish anything on this technique[10]. I was not particularly proud of the concept, for it seemed to me to be the obvious gaseous analogy of gradient-elution liquid chromatography which had recently been invented by Williams and others. I was even stupid enough not to consider patenting the idea, and so avoided the perils of becoming a millionaire. However, my real point is that temperature-programmed chromatography was then independently invented by at least three other groups, the chief investigator of the last being awarded a medal for his discovery.

I have already mentioned examples of *forgotten* discoveries in the history of chromatography, including chromatography itself and gas–liquid chromatography. We must suspect that there are many others and someone not driven foreward inexorably by the brilliance of his own thinking might well find it profitable to peruse some of the older literature for clever ideas that have never been properly developed. My own favourite here is the paper on "Electron attachment spectroscopy" by Lovelock *et al*[11], which as I understand was never followed up because of difficulties with technical assistance in Houston, which outsiders could never believe. I have also over the years been impressed by the bandwagon effect in chromatography, which tends to carry most practioners along whatever road is currently in fashion. I would suggest in particular that the non-analytical aspects of chromatography have been somewhat neglected, while the reproducibility and taxonomy of the subject has not yet been developed so as to make chromatography the standard physico-chemical tool it might be.

I believe it was Mark Twain who pointed out that while everyone would talk about the weather, nobody actually seemed to be doing anything about it. To some extent it is the same with scientific discovery. Martin began his Nobel lecture in 1951 with these words: "If enough histories, written while the ideas are still fresh in the minds of the peoples concerned, are available for a variety of discoveries of inventions, it may eventually be possible to lay down some of the principles required to facilitate the obtaining of fruitful results in scientific research in general. Clearly also the background of knowledge at the time the advance was made will be best understood if the history is as recent as possible." This will be the main theme of this paper.

How then are discoveries made? I believe, contrary to what most philosophers seem to have supposed, that there is no one royal road: there are many different ways of making discoveries but certain circumstances reappear with sufficient regularity to suggest that they might be useful as guides. The first perhaps is the need to solve a *problem*. We cannot imagine that Archimedes was the first to cause his bath to overflow. When Pavlov was asked by his students how they might become as inventive as he was, his reply is quoted as "Get up in the morning with your problem before you. Breakfast with it. Go to the laboratory with it. Eat your lunch with it. Keep it before you after dinner. Go to bed with it on your mind. Dream about it." In a somewhat different context Lenin is said to have made similar remarks about a revolution. Tswett and Martin were both brought to chromatography to solve specific problems, and this seems to have been the case with the vast majority of the classic chromatographers. In fact they were not prone to call themselves chromatographers or even analytical chemists but biochemists, chemical engineers or medical researchers.

Cross-fertilisation seems also to play a frequent role in scientific discoveries. Many if not most of the chromatographic advances have been made by those who have come into the field from outside. Furthermore, the rapid advance of chromatographic methods has been enhanced by the readiness with which ideas were exchanged. Martin himself set the tradition (see for example the remarks of Scott[12]) but the banner was readily taken up by the Chromatography Discussion Group under Desty and of course by the series of conferences organised by Zlatkis of which this is the Jubilee.

Analogy can often be useful. I have referred above to the analogy of partition chromatography and counter-current processes, and of temperature programming and gradient elution. High-performance liquid chromatography seems to have been created at least in part by out-of-work gas chromatographers, who wondered why they should not be able to get similar high efficiencies with flowing solvents as with flowing gases. But analogy is not always right, and the early years of gas chromatography were plagued by low pressures at column outlets because this is what one did in distillation.

Simplicity has its philosophical counterpart in Occam's razor, but is beautifully exemplified in chromatography where the crucial ideas can be explained without complexity and even to the layman. *Relaxation* or turning aside from the immediate problem has often been scientifically productive. Kekulé is said to have mused about chemical structures in front of the fire and on the top of the Clapham omnibus. Heisenberg arrived at the essentials of his quantum matrix mechanics while he was escaping from hay fever by the sea at Heligoland. There must be parallel examples in chromatography, but I have not been made aware of them. However, little seems to have been achieved without *hard work*, despite the simplicity which eventually results. Many of us have had the experience of thinking up but not thoroughly developing an idea, which is then later done properly by others. For me pheromones is a case in point.

Observation is crucial. I have had more or less the same experience with all new research students and over some forty years. They expect to get a certain result; usually I have to admit a result that I have suggested. When they do not get it, their first reaction seems to be to do the experiment again. Of course they should check to see whether they have made some simple mistake, but they should also consider (and this seems to strike most of them as quite bizarre) that they may have observed something essentially new. I once had a pupil who was an unusually inept experimentalist. He was studying the catalytic polymerisation of olefins, but could never inject the same amount from one experiment to the next. To overcome this difficulty I proposed that he worked with a standard mixture of olefin and an inert paraffin marker. He soon had the paraffin polymerising as well, and would not take no from me as his answer. His insistence led us to investigate further and we were thus able to uncover some slow diffusional processes. Later I published a note on this, and was very interested to find that a number of other research supervisors had been presented with similar observations, but by less determined students. Or as Hesse quotes Professor Meerwein about a colleague: "The poor man is too educated. As soon as he has an idea, he immediately knows why it should not work, and therefore he never tries anything"[13]. Observation however needs to be *careful* observation. Many years ago we were measuring some thermodynamic effects by gas chromatography. This required precise control of column temperature which we set out to achieve with vapour baths. Stupidly I forgot that vapour purity was not enough so that the final calculations provided a greater scatter than we had hoped for. Then the penny dropped, but fortunately my student had indeed been very careful and had noted the exact times of all his measurements. We were thus able to correct for the atmospheric variations in pressure by reference to the Geography Department of the University which has kept detailed records in Oxford over many years.

Then there is *serendipity*, a feature which I have found stressed by nearly all scientists that I have spoken to about their discoveries. Martin claimed that it was the accidental presence of 1% ethanol as stabiliser in his chloroform solvent that prevented the amino acids remaining at the top of his column[14]. The argon-ionisation detector, so Lovelock tells us, was discovered because the stores had temporarily run out of cylinders of nitrogen[15]. Porath's work on size-exclusion chromatography began with some electrophoretic experiments in which the current by neglect had not been switched on[16]. Hollis, as I recall, developed porous polymers as stationary phases for gas chromatography because he chose by accident to investigate first the only suitable polymer from a range which he had been sent in the hope that he could find something for which they might be useful. Ettre[17] claims that his entry into chromatography was a result of his being falsely identified as an analytical chemist. Giddings[18] traces his theoretical contributions to chromatography to the curious chance of his being instructed to go into chromatography by Henri Eyring at a time when he had just been taking a graduate class on the "Principles of physical statistics". The technique of stopped-flow chromatography[19] turned out to be much better than I had expected, because I had not fully thought out the functions of the chromatographic column: at times it can be fortunate that it is so easy to do experiments in chromatography.

On *fraud* and *error* it is perhaps wise to pass, but I suspect most of us have found it difficult to repeat exactly the work of others.

Rejection seems to be the natural fate of many good new ideas. We think perhaps of Tswett, but most of us were discouraged in our early efforts at chromatography. Gerhard Hesse[13] relates that the disbelief in chromatography in Munich in 1930 was so well established that he was angrily instructed by his supervisor Wieland to "stop this stupid thing". I too was very pointedly told that I was wasting my time, until I was rescued by a visit from some chemists in ICI, and I understand that Howard Purnell was thought by Professor Norrish to be going down a mere bypath[20]. Evan Horning was strongly opposed by scientists and scientist administrators in his desire to introduce the new ideas and new techniques of chromatography into medical research[21]. When Keene Dimick started the Aerograph company (through which he was later to become of course a millionaire) it was treated as something of a joke by his colleagues in government service who were convinced he would soon be back with them again[22]. In response to Michael Lederer's proposal to Elsevier that there should be a journal for chromatography, the director was far from enthusiastic and wondered "would this chromatography last?"[23]. The referee of the paper by Zlatkis and Lovelock which combined capillary chromatography with a sensitive ionisation detector was anxious to reject it as the chromatograms were too good to be real[15]. I was told that he suspected they had been drawn with a ruler.

Many discoveries (like Columbus) arise because someone looks where no one has looked before or, in science particularly, because of the advent of a new tool such as the telescope, the microscope or microwave technology. For Tswett (quoting Descartes) "every scientific advance is an advance in method". Jack Kirkland[24] traces his enthusiasm for chromatography to the fact that Dal Nogare was able in three hours to solve a problem which had been bugging him for many weeks. "Sandy" Lipsky[25] recorded his own conversion when he read an article by Martin in the *Biochemical Journal* which described the separation of the fatty acids, a problem with which he had long been wrestling. I remember that many years ago we showed[26] how it was possible to identify a whole string of volatile silanes (the silicon analogues of the alkanes) by gas chromatography. The work rippled few Anglo-Saxon waters, but one of my research students found later that he had saved the reputation of a young continental colleague who had claimed to have made iso-silobutane, which the "great Professor Stock had failed to make many years before".

Now I have tried to suggest that it is important to know the way in which discoveries are actually made. There is indeed something of an anthropology of science which will be lost if no attempt is made to preserve it. This means therefore that some record should be kept of the discovery process as well as the discovery itself, although this flies in the face of all the recent traditions of the scientific literature. In particular the editors of scientific journals, no doubt correctly worried by their problems of space, strongly discourage such a procedure: they seem trained to prefer the supposedly rational to the real. Philosophers were long eager to explain how science was done, but more recently they seem to have given up the ghost of even telling us how it should be done: they concern themselves more and more with only the logic of testing and proof. Thus it is only scientists themselves who can really tell us what is done. But why in particular chromatographers? Why you?

To my mind there are at least six good reasons. Firstly and most obviously, chromatography has been my own specialist interest and clearly among the interests of you my audience. Secondly, while I have always found that chemistry is a glorious conversation stopper, chromatography and what chromatography does is something that one can, without too much difficulty, explain to the traditional man or woman in the street. I believe it should play a much larger role in chemical education, a point I have laboured elsewhere[27]. Moreover, thirdly, our subject lies at the very heart of chemistry, a theoretically unreal realm since it is concerned with the properties of pure substances, which like vacua and for essentially the same reason are abhored by nature. I remember Keulemans pointing out to me that the Dutch have it right when they call chemistry "scheikunde" (the art of separation). Fourthly, as I have already indicated, the traditions of chromatography involve the ready, frank and honest exchange of ideas. Fifthly, it is a subject that is still very alive and vigorous. The problem so often with the history of science, and especially for scientists, is that it is difficult for us to recast our minds into the ways of thinking of a past age. Who could now resurrect the full awe of the Pythagoreans who seem to have been the first to recognise that numbers play a role in natural phenomena or the theological restraints that bedevilled Newton and Darwin? When Richard Trevithick first contemplated using a steam engine as a locomotive, he had seriously to consider whether it really would be possible to use a wheel to provide traction rather than merely roll along behind traction. Apparently he only became convinced after he and a friend had removed the horse from a cart and demonstrated to themselves that it could be moved uphill by turning the spokes by hand[28]. Also of course we no longer have access to all the relevant facts: they are conveniently but misleadingly replaced by imagination. Sixthly, I would wish to suggest that for most of us the more mundane discoveries are actually more significant than the Kuhnian paradigms: they are so much more like the discoveries that scientists actually make. It may even be that the Newtons, the Einsteins and the Martins are a race apart with their own peculiar roles: though I have to admit that I doubt it. Moreover one of the problems with famous discoveries is that they have been too often enquired into; they tend to generate myths. Mendel and Tswett are probably examples. Certainly it has been shown that Fleming could never have discovered penicillin in the way he later described[29].

The study of chromatography also raises the intriguing question whether there may be other simple techniques which we are missing, and which later generations will regard as curiously obvious. Or is the whole of scientific research a little like oil: something of a wasting asset from which we have been particularly fortunate to benefit?

ACKNOWLEDGEMENT

I would like to express my gratitude to L. S. Ettre for his most helpful comments and criticism.

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