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The Cover ... Watercolor, girl evaporating a solution, St. Paul's School for Girls, London, 1930s. See p. 131.

KINETIC VERSUS THERMODYNAMIC CONTROL: SOME HISTORICAL LANDMARKS

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The study of chemical reactivity may be broadly divided into the subject areas of reaction stoichiometry, reaction kinetics, and reaction thermodynamics. The first deals with the classification of chemical reactions, their expression as properly balanced net chemical equations, and the various quantitative calculations that are based upon these balanced equations. The second deals with the determination of rate laws and the deduction of reaction mechanisms, while the third deals with reaction efficiency and chemical equilibrium as a function of the relative stabilities of the various reactants and products, their concentrations, and the ambient temperature and pressure. In more colloquial terms, these three subject areas deal with the theoretical answers to the questions of “What changes in a chemical reaction?,” “How fast does it change?,” and “How complete is the change?”

Obviously the proper differentiation of these three questions and their resulting areas of specialization only gradually evolved over time. Thus the distinction between questions two and three was probably not complete until the 1880s with the rise of chemical kinetics and chemical thermodynamics as distinct subdisciplines, as personified by the publication of van't Hoff's classic monograph, *Études du dynamique chimique*, in 1884 (1). The key steps in this differentiation are at least implicitly covered in most standard histories of chemistry and it is not our intent to repeat them here. Rather our goal is to trace the subtle manner in which these questions once more became entangled with one another when dealing with the pervasive problem of competing

chemical reactions, only to gradually separate once more under the rubrics of kinetic versus thermodynamically controlled chemical reactivity. As we will see, this pertinent distinction was independently discovered at least three times—each time within a different field of chemistry—thereby also providing us with a cautionary tale concerning the importance of the role played by textbooks and university curricula in the preservation and transmission of chemical knowledge, not to mention the perils of overspecialization.

The Laws of Chemical Affinity

Though there are scattered precedents in the 17th century, the first attempts to systematically study and classify chemical reactivity really date from the 18th century and came to constitute what became known as the study of “chemical affinity.” This same century also saw the famous chemical revolution of Antoine Lavoisier and his collaborators, which focused instead on the subjects of chemical composition and changes of state. Though Lavoisier fully recognized that the study of chemical affinity was a legitimate and important field of chemical investigation as well, he also felt that it was still too immature and imperfectly developed for coverage in an elementary textbook and, for this reason, purposely chose not to include a discussion of its results in his famous *Traité* of 1789 (2).

So significant was the impact of Lavoisier's revolution for the subsequent development of chemistry that

on a similarity in the properties of the reactants (law 2) and that the properties of the reaction products were an average or blending of those of the starting materials (law 3)—ideas which he had, in turn, probably absorbed from Georg Ernst Stahl's *Fundamenta chymiae* of 1723.

Some indication of the progress made in the study of chemical affinity during the century may be gleaned by comparing Macquer's seven laws of 1749 with the eight laws of chemical affinity given by the French chemist, Antoine-François de Fourcroy (Figure 3), 33 years later in his own textbook of 1782, where the second and third of Macquer's laws are directly contradicted by the first and sixth of Fourcroy's new laws (10):

1. The attraction, or affinity of composition, cannot act but between bodies of different natures.
6. Two or more bodies united by the attraction of composition, form a substance, the properties of which are different from those which each of the bodies possessed before their union.

—versions which the modern chemist hopefully will recognize as being far closer to our current views on the nature of chemical change than those of Macquer.



Figure 3. Antoine-François de Fourcroy (1755-1809).

But what is far more pertinent to our present inquiry is Fourcroy's seventh law of chemical affinity, which reads (10):

7. The attraction of composition is measurable by the difficulty of destroying the combination formed between two or more bodies.

At first glance this may seem irrelevant to the question of kinetic versus thermodynamic control, but on reading Fourcroy's commentary on this law we quickly discover the following statement (10):

We find it as particularly necessary to insist upon this law because beginners are apt to fall into mistakes when estimating the differences of the attraction which unites the principles of different combinations. From the rapidity with which some substances combine, we are ready to imagine that their mutual attraction must be very considerable. But long experience shows that the eagerness to enter into combination, instead of indicating a perfect composition, is rather proof that the attraction between the bodies is extremely weak, and can produce but a very imperfect compound. In order, therefore, to determine accurately the degree of affinity with which bodies unite and remain in union, we must consider the ease or difficulty with which they are separated.

Both the identical law and a similar commentary appear in the discussion of affinity found in Fourcroy's more elaborate, 11-volume, chemical treatise of 1801, in which his list of affinity laws has been expanded from eight to ten (11):

By attention too immediate to the first appearances, chemists have supposed that those bodies which combine the most speedily or with the greatest quantity of motion, have the strongest affinity for each other; with these chemists the speed of combination became the measure of affinity. It has long been ascertained that this is a source of error and delusion. It often happens, on the contrary, that such substances as are with the most difficulty brought into combination are those which adhere the most strongly to each other. Whence it results that the true and only exact method of determining the force of chemical attraction between bodies is to measure the force we are obliged to employ to separate the constituent parts of a compound.

These two statements are, to the best of my knowledge, the first explicit recognition that there is an important distinction to be made between the speed of a chemical reaction and the stability of the resulting products or, in modern terms, between chemical kinetics, on the one hand, and chemical thermodynamics on the other. And it further implies that there is often, but not always, an inverse relationship between the two.

Though none of the modern historical studies of affinity theory mentioned earlier seem to have called attention to the importance of this observation, several of Fourcroy's contemporaries did and dutifully reproduced versions of it in their own textbooks. Thus the 1819 edi-

tion of John Murray's four-volume *System of Chemistry*, which was published nearly a decade after Fourcroy's death, contains the statement (12):

The facility or rapidity of combination depends not on the force of affinity, but on that modified by the cohesion, elasticity, and other qualities of bodies; and we have many examples in which a combination takes place slowly where the attraction from which it arises is strong, or where it is affected with facility, where the attraction is comparatively weak.

Similarly, 23 years later we find a related statement in an 1842 paper by the French chemist, Joseph Louis Gay-Lussac (Figure 4), on the complex aqueous solution chemistry of the oxosalts of chlorine (13):

It is a general rule that, if one is able to form, at the same time and with the same elements, various compounds that are unequally stable, but capable of existing under the same circumstances, then it is the least stable that is formed first. If the circumstances change or are impossible to maintain, the compound of intermediate stability succeeds it and so on until one has arrived at the most stable compound or the component elements are separated.

Note that this statement actually goes one step beyond Fourcroy's original law by applying it, not just to the formation of single products, but to a reaction system capable of forming several distinct sets of competing products. Though Gay-Lussac makes no mention of Fourcroy, it is not improbable that he was fully aware of Fourcroy's law from a reading of his treatise of 1801 since Gay-Lussac was only 23 years old at the time and in the midst of his formative student years when it was first published.



Figure 4. Joseph Louis Gay-Lussac (1778-1850).

The Demise of Affinity Theory

By the late 1850s the original outlines of classical affinity theory had begun to fade. The first facet to go was the affinity table, whose underlying assumptions had been severely undermined by the work of the French chemist, Claude Berthollet, at the turn of the century, on the influences of both changes of state and mass action effects in modifying the outcomes of the displacement reactions which had formed the basis of such tables in the first place (14). By 1819 the value of these tables was already being seriously questioned by the ever-thoughtful Murray in his masterful textbook (12):

From the preceding observations it must be apparent that the common tables of elective attractions do not represent the relative forces of affinity, but only a series of decompositions, which arise as much from the operation of circumstances which influence attraction, as from differences in the strength of the power itself. Nor do they even express the order of these decompositions accurately, since the influence of quantity, which undoubtedly modifies the results to a certain extent, has been neglected in the experiments on which they are founded. They are therefore of less utility than has been believed.

The second facet to disappear was the affinity diagram. Despite the rule set down by Fourcroy in his seventh law, chemists had in fact never agreed on the proper method for measuring chemical affinity, let alone on how to relate such measurements to the hypothetical numerical interparticle force values given in the typical affinity diagram. Thus, for example, the French chemist, Guyton de Morveau, attempted to correlate the affinities of various metals with the force required to separate a disk of the metal in question from a mercury surface; whereas the German chemist, Carl Wenzel, attempted to correlate them with the time required to dissolve a cylinder of the metal in acid; and the Irish chemist, Richard Kirwin, with the weight of an alkali or metal required to saturate a given amount of acid.

With the gift of hindsight, we now know that all of these attempts were fundamentally flawed. Guyton was actually measuring intermolecular forces (called "attractions of aggregation" by 18th-century chemists) rather than the interatomic forces (or "attractions of composition") actually responsible for compound formation; Kirwin was conflating chemical composition with chemical affinity and was actually measuring combining weights; whereas Wenzel was conflating kinetics with questions of stability. Indeed, there is little doubt that Fourcroy's commentary on the inverse relationship between speed of

reaction and chemical stability was specifically intended as a criticism of the work of Wenzel, as summarized in his 1777 monograph *Lehre von der Verwandtschaft der Körper* (15).

Nevertheless, it should be noted, that, while the use of hypothetical force values had largely disappeared from reaction diagrams by the 1820s (only to be replaced in many cases with stoichiometric equivalent weight values instead), chemists continued to use these diagrams, now reinterpreted to show only which components had interchanged places in a reaction, well into the 1860s, when they were finally fully displaced by the use of balanced linear equations (8).

Of the three original affinity formats, it was the so-called laws of chemical affinity that managed to survive the longest in the textbook literature. Thus, in his popular textbook of 1858, the American chemist, David Wells, was still listing nine laws of chemical affinity, several of which echoed the more significant innovations found in Fourcroy's original list, including both Wells' third and fourth laws (16):

3. Generally speaking, the greater the difference in the properties of bodies, the greater is their tendency to enter into chemical combination. Between bodies of similar character, the tendency to union is feeble.
4. Chemical affinity occasions an entire change in the properties of the substances acted upon.

However, no trace can be found of Fourcroy's seventh law or of its concomitant observations on the inverse relationship sometimes found between speed of reaction and product stability nor of Gay-Lussac's later elaboration. The reasons for this disappearance are not hard to surmise. With the demise of the affinity table and the temporary abandonment of the experimental program to measure affinity values, there was no longer any need for a rule to govern their measurement. As for the still valid observations on the distinction between speed of reaction and product stability, the baby was simply thrown out with the bath water and became an artifact of an outdated literature that most chemists no longer read.

The Study of Phase Transitions

One of the defects of Fourcroy's original statements of his rule concerning speed of reaction and product stability was his failure to provide concrete examples of its application to actual reaction systems, and much the same may be said of Murray's later discussion as well, though he did provide a physical example involving the separation of solids from cooled liquids and solutions (12):

When attraction of aggregation is exerted, the particles are sometimes united indiscriminately, so as to form irregular masses; sometimes they pass into arrangements, whence masses of regular figures arise. The former happens generally when attraction is exerted suddenly, and with considerable force. If a liquid be suddenly cooled to a sufficient extent, a mass is formed altogether irregular. Or if a substance be produced by chemical action, the particles of which have a strong mutual attraction, this is exerted at the moment of its production, and it is separated in the form of a powder. This latter case is named in chemical language Precipitation, and the substance is said to be precipitated. The other result occurs when aggregation, previously weakened either by the operation of heat or of chemical attraction, resumes its force more slowly. The particles then assume a particular arrangement so as to form masses of regular figures, or bounded by plane surfaces and determinant angles. The result is named Crystallization, and such regular figured masses are denominated Crystals.

Of course there seems to be only a tenuous relationship at best between the issue of crystal size and the issue of product stability required by a literal reading of the original law, and we must now move forward another 70 years, and switch from the study of chemical affinity to the newly emerging field of phase science, in order to reestablish the necessary connection, as found in a paper published in 1897 by the German physical chemist, Wilhelm Ostwald (Figure 5), entitled "Studies on the Formation and Transformation of Solid Bodies" (17).

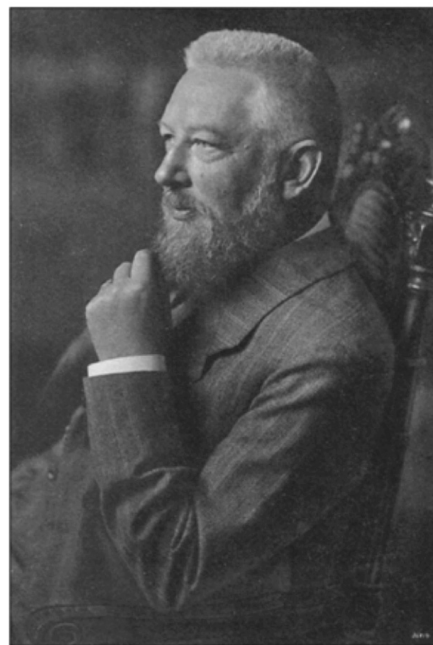


Figure 5. Wilhelm Ostwald (1853-1932).

As suggested by the paper's subtitle, "Supersaturation and Supercooling," Ostwald was interested in the phenomenon that rapidly cooled gases, liquids, and solutions often persisted long after they had ceased to be thermodynamically stable and, when finally transformed into a more stable solid capable of existing in two or more polymorphic modifications, often initially selected the least energetically stable of these possible alternatives rather than the most stable. Halfway through his lengthy 42-page article, Ostwald paused and attempted to generalize—albeit rather awkwardly—these observations in the form of a tentative law:

... I would like to summarize our experiences so far concerning this subject with the general law that, on leaving any state and passing into a more stable one, that which is selected is not the most stable one under existing conditions, but the nearest.

Known sometimes as Ostwald's "law of successive reactions" or "successive transformations" and sometimes as the "Stufenregel" or "rule of stages," it was far more clearly articulated several years later in the 1912 edition of his popular textbook, *Outlines of General Chemistry* (18):

If the metastable region has been exceeded, and a new phase appears spontaneously, it is remarkable that the phase which appears is not the most stable phase under the conditions, but is the least stable, i.e., the next in stability to the phase undergoing the transformation.

A second by-product of Ostwald's work in this area was the establishment of much of our current terminology for dealing with such phenomena. In the 1895 edition of *Outlines of General Chemistry* he had explicitly complained of the absence of a suitable vocabulary (19):

Such phenomena have been mostly considered as being to a certain extent unnatural, and the corresponding states have received the names of superheating and overcooling or supersaturation. They are nevertheless very common, and appear whenever, from a substance or mixture of substances in a homogenous state, a part may separate out; thus, for example, gases, solids, or immiscible liquids from liquids, or, on the other hand, liquids or solids from gases. The name "states of instability," which has also been applied in such cases, is equally unsuitable. For the states are not really unstable, since they by no means pass into others on the smallest change. This must rather be compared to the stable equilibrium of a rather tall cylinder standing on one end; the system is certainly stable, but when it suffers a somewhat large displacement it easily assumes another state which is much more stable than the first. It must be

admitted, however, that here there is no analogy to the special action exercised by a small quantity of the heterogeneous substance [i.e. a seed crystal] in all the cases above mentioned.

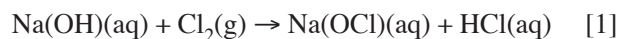
The term "false equilibria," favored by the French physicist, Pierre Duhem, was not much better (20). However, in his 1897 paper Ostwald finally suggested use of the term kinetically "labile" to describe systems that rapidly underwent the necessary phase change upon reaching their thermodynamically proscribed limits, versus use of the term kinetically "metastable" to describe those that persisted beyond that point and which, in the words of Findlay, exhibited the phenomenon of "suspended transformations" (21).

Though exceptions to Ostwald's rule are known, both it and Ostwald's proposed terminology soon found a place in the first generation of physical chemistry texts (22)—perhaps not surprisingly given that many of them were written by Ostwald's former students—as well as in the advanced monograph literature dealing with both the phase rule (21, 23) and with polymorphism (24-26), though neither of these topics have ever loomed large in the education of the average chemist.

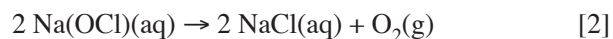
In his later account of 1912 Ostwald also went one step further (no pun intended) and asserted that his rule applied not just to phase transitions but to chemical reactions in general (18):

... This phenomenon is quite general in character, and is not limited to equilibrium of the first order, but holds in all changes of state, and especially in chemical reactions in the strict sense.

This assertion he further illustrated in the 1908 edition of his textbook, *Principles of Inorganic Chemistry*, using the reaction between aqueous sodium hydroxide and dichlorine gas (27). This initially produces the compound known as sodium hypochlorite or Na(OCl):



However, if this is allowed sufficient time, it will eventually decompose into the thermodynamically more stable products of sodium chloride and dioxygen gas:



thereby illustrating the rule of stages (27):

It might now be asked why hypochlorite is formed at all, and why the whole amount of the substances doesn't straightway pass into the most stable condition, chloride and oxygen ... The answer to this question is again afforded by a general law, which states that in all reactions the most stable state is not

straightway reached, but the next less stable or that state which is the least stable of the possible states. Starting from this, the more stable states are reached one after the other, and the process of transformation comes to a stop only when a state is finally attained which cannot further change and is, therefore, the most stable.

Indeed, Ostwald was quick to point out that the situation was even more complex than this, since in actual fact several additional transient reactions intervened between reaction 1 and reaction 2, leading to the formation of such products as sodium chlorate or $\text{Na}(\text{ClO}_3)$ and sodium perchlorate or $\text{Na}(\text{ClO}_4)$ —a situation which he illustrated by means of the free-energy diagram shown in Figure 6.

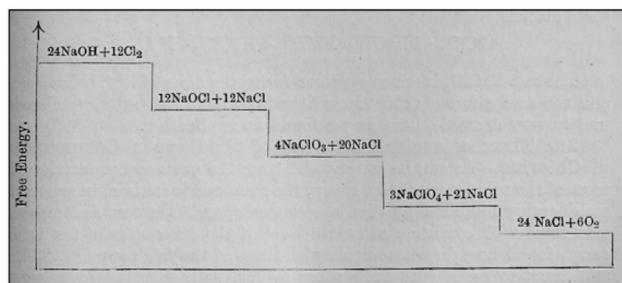


Figure 6. Ostwald's diagram of 1908 illustrating the successive stages in the reaction between $\text{Na}(\text{OH})(\text{aq})$ and Cl_2 as a function of free energy content (27).

I have been unable to uncover any evidence that Ostwald was aware of Gay-Lussac's earlier statement of 1842. By the 1880s the traditional field of chemical affinity had clearly bifurcated into the newer fields of chemical kinetics versus chemical thermodynamics and there was little motivation for the new generation to consult the outdated paradigms of the older affinity literature. Yet it is certainly curious that Ostwald chose to illustrate the application of his rule to chemical reactions proper using the exact same reaction system as Gay-Lussac had used 66 years earlier!

Transition States and Potential Energy Surfaces

We now fast forward yet another half century and switch from the field of phase science to the field of physical organic chemistry and to a paper published in 1944 by R. B. Woodward (Figure 7) and H. Baer on diene-addition reactions (28). In studying the Diels-Alder addition between 6,6-pentamethylenefulvene and maleic anhydride, they found that a mixture of both the *endo*-

and *exo*- isomers was obtained for the resulting addition product (Figure 8). Initially labelled as the *α-adduct* and *β-adduct*, respectively, these two isomers were found to have quite distinctive physical and chemical properties and to be preferentially favored or disfavored by certain changes in the reaction conditions (28):

... allowed to react in benzene solution, at room temperature, an *α*-adduct, $\text{C}_{15}\text{H}_{16}\text{O}_3$, m.p. 132° , is obtained. If, however, the mother liquor from the recovery of this product is allowed to stand for several weeks, very large beautiful crystals of a new, *β*-adduct, $\text{C}_{15}\text{H}_{16}\text{O}_3$, m.p. 93° , gradually separate. Further, as the initial condensation is carried out at higher temperatures, the formation of the *β*-adduct takes place more rapidly, and less of the *α*-adduct is obtained.



Figure 7. Robert Burns Woodward (1917-1979).

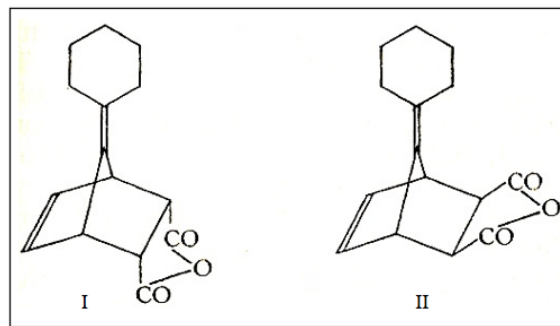


Figure 8. The structures of the *endo*- (I) and *exo*- (II) isomers for the product formed on reacting 6,6-pentamethylenefulvene with maleic anhydride (28).

With the development of absolute rate theory in the 1930s by Eyring in the United States and by Evans and Polanyi in Great Britain (29, 30), Woodward and Baer had access to a new set of theoretical concepts for the rationalization of reactivity—such as potential energy surfaces, activation barriers, and transition states—that were largely unavailable to Ostwald in 1897. In order to rationalize their results Woodward and Baer made use of these newer tools by postulating the potential energy surfaces shown in Figure 9 in which the rapidly formed *endo*-isomer was assigned a lower activation energy and hence faster kinetics than the *exo*-isomer, but in which the two surfaces crossed before reaching final equilibrium, thereby ultimately making the *exo*-isomer the thermodynamically favored product. Most of the rest of the paper was devoted to experimentally establishing which adduct corresponded to the *exo*- and which to the *endo*-isomer and to electronically and stereochemically rationalizing why the *endo*-isomer might be expected to have a lower activation barrier than the *exo*-isomer.

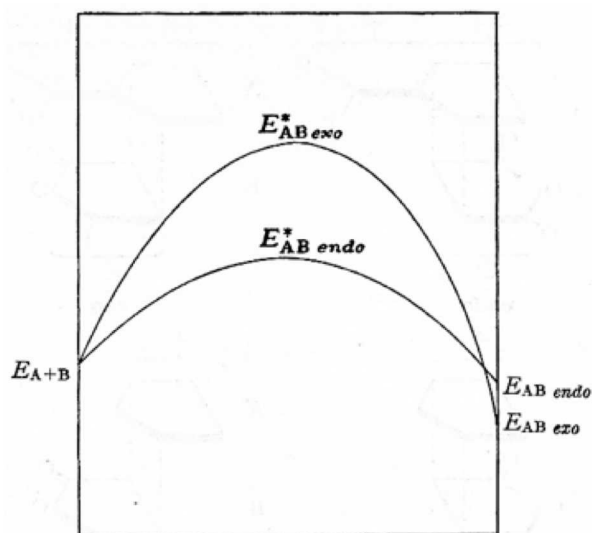


Figure 9. Potential energy diagram used by Woodward and Baer to rationalize kinetic versus thermodynamic control in diene-addition reactions (28).

Though Woodward and Baer did not use the terms kinetic control versus thermodynamic control in their paper, this is still, to the best of my knowledge, the first implicit use of these concepts in the field of organic chemistry, and their experimental observations may be generalized using this terminology by the general rule that:

Low temperatures and/or short reaction times favor kinetically controlled reactivity, whereas high temperatures and/or prolonged reaction times favor thermodynamically controlled reactivity.

As for the terms themselves, they appear to have been first used in the 1956 edition of Jack Hine's textbook, *Physical Organic Chemistry* (31), though it would take another three decades for them to become standard textbook fare. Thus, no mention of them is to be found in an index search of the physical organic texts by Wiberg (1964), Wheeler (1966), Kosower (1968), Hammett (1970), Ritchie (1975) or Jones (1984) and their coverage in the text by Hirsch (1974) is incidental (32). On the other hand, they are employed in the later texts by Lowry and Richardson (1981), Klumpp (1982), Maskill (1985) and Isaacs (1987) (33). Likewise, a computer search of the index for *the Journal of Chemical Education* using the search term "kinetic control" revealed roughly 55 entries, starting very sporadically in 1965 and rapidly increasing only during the last two decades, dealing with laboratory experiments, lecture demonstrations, clever teaching analogies (see Figure 10), and popular overview articles related to this topic.

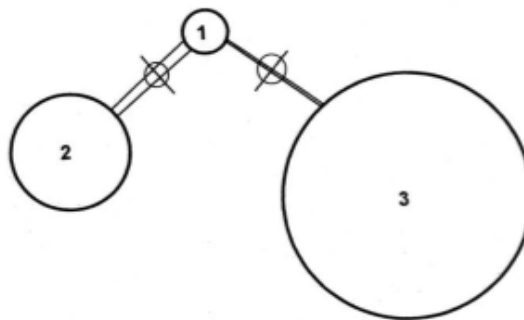


Figure 10. An ideal gas analogy for kinetic versus thermodynamic control proposed by Macomber in 1994 (34). Two evacuated flasks (2 and 3) of unequal volumes are connected to the smaller flask 1 containing an ideal gas. The tube connecting 1 and 2 is 10 times the diameter of that connecting 1 and 3. On quickly opening and closing the two stopcocks the quantity of gas in flask 2 is found to be greater than that in flask 3. This is kinetic control. On reopening the stopcocks permanently, the pressures in all three finally equalize, such that the quantity of gas in 3 is now greater than that in 2. This is thermodynamic control. The volumes of the flasks are analogous to the inverse of their free energy content and hence to their positions on an energy-reaction coordinate plot.

The expected time evolution for the system shown in the potential energy plot in Figure 9 is shown in the extent of reaction (ξ) - time (t) plot in Figure 11, where, if the reaction is terminated at time $t_1 < t_{eq}$, where t_{eq} is the time required to reach equilibrium, the major product (P') is kinetically controlled, whereas, if it is terminated at $t_2 > t_{eq}$, the major product (P) is thermodynamically

controlled. ξ_{\max} denotes the stoichiometrically allowed maximum for the extent of reaction parameter as determined by the concentration of the limiting reagent. Of course, the phrase “terminate the reaction” implies that it is possible to alter the reaction conditions such that any further conversion of the kinetic product into the thermodynamic product is completely inhibited, and it becomes possible to isolate the kinetically metastable product and store it in a bottle indefinitely. In the case of the room temperature Diels-Alder addition studied by Woodward and Baer, this was accomplished simply by eliminating contact with the solvent, whereas in high-temperature reactions it is usually accomplished by the act of rapidly cooling the kinetic product to room temperature.

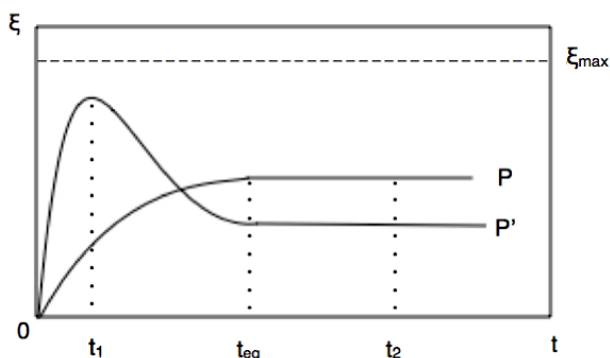


Figure 11. An extent of reaction - time plot for the competitive formation of a kinetically controlled product (P') versus a thermodynamically controlled product (P).

From Isomers to Polymorphs

In sharp contrast to the situation in the field of physical organic chemistry, it took a surprisingly long time to arrive at a satisfactory theoretical rationale for Ostwald's law of stages in the field of phase science—a situation not helped by Ostwald's well-known disdain for the atomic-molecular theory. One such early attempt was made in 1913 by the Dutch phase scientist, Andreas Smits, using his ill-fated theory of allotropy (35). This postulated that the homogeneous phases of all pure substances, including crystalline solids, were in fact homogenous mixtures of rapidly interconverting molecular clusters of various sizes, known as “pseudo-components.” As long as the rate of these interconversions was greater than that for a particular phase change, they had no effect on phase behavior and the substance in question continued to behave thermodynamically as though it had only one component. However, if for some reason, one or more of these cluster interconversions was kinetically inhibited

or slowed down in some way, then the substance would begin to display complex phase behavior more typical of multicomponent systems.

In applying his theory to the question of which of several alternative product phases was selected in a polymorphic phase change, Smits assumed that the situation was in fact competitive. Each possible product phase was determined by a particular cluster present in the reactant phase and the question of which product formed first was reduced to the question of which of these competitive alternatives was present in the greatest concentration at the transition point.

By 1925 the German phase scientist, Gustav Tammann, building on work extending back to the 1890s (36), was advocating a related picture based instead upon the formation of centers of nucleation or crystallization in the liquid or gas phases rather than on hypothetical fluctuating molecular clusters. Once again the process was envisioned as being competitive, with the reactant phase at the moment of actual transition containing nuclei for all of the possible solid product phases and the actual solid phase selected being, in turn, determined by their relative concentrations and/or rates of formation (21):

Inasmuch as the process of spontaneous transitions is an atomic one it will be subject to the laws of probability. Therefore, only the probability of formation of crystal centers, the forms of which have different stability, may properly be discussed ... Ordinarily grains of the forms with different stability appear simultaneously.

In 1933 Stranski and Totomanow attempted to test this hypothesis by calculating the relative numbers of different nuclei present in the melts for two example dimorphic systems as a function of temperature and various structural parameters for the product phases using an equation that had been recently proposed by Volmer (37, 38). For the $\text{NaBr} \cdot 2\text{H}_2\text{O}$ system the more stable polymorph had the greatest nuclei abundance and thus violated Ostwald's rule upon solidification, whereas for the HgI_2 system the less stable yellow polymorph had the greatest nuclei abundance and thus obeyed Ostwald's rule upon solidification.

It was, however, not until the 1990s that the concepts of kinetic versus thermodynamic control and a potential energy surface (Figure 12) similar to that originally proposed by Woodward and Baer in 1944 to rationalize competitive isomers were finally applied to Ostwald's *Stufenregel* and the rationalization of competitive polymorphs, allowing the rule to be reformulated as:

When a solid capable of polymorphic modifications separates from a liquid or gas, the polymorph which is initially deposited is metastable relative to the other potential products and is therefore kinetically rather than thermodynamically controlled.

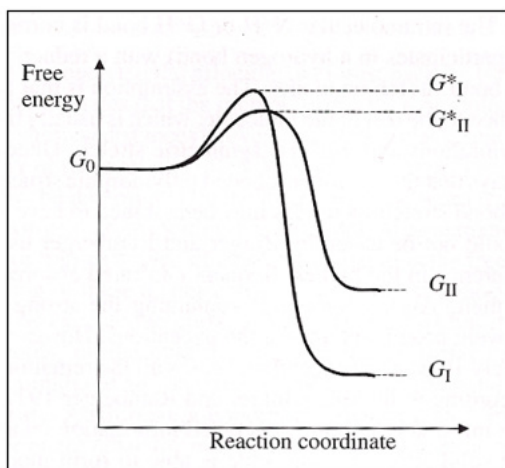


Figure 12. The free-energy surfaces used by Bernstein (26) to rationalize Ostwald's law of stages in terms of kinetic versus thermodynamically controlled reactivity.

Furthermore, any apparent exceptions could now be rationalized as cases for which the existence domain for the initial metastable product is so narrow that it is passed through without detection in favor of the more stable product.

It is important to remember that the competitive situation assumed by all of these models applies to the gas or liquid at the point when the first solid phase separates and not necessarily to the subsequent transformation of that solid into more stable modifications. Unlike the competitive formation of isomers dealt with in organic chemistry, in which the various alternative products are simultaneously formed and only their ratios change on moving from the realm of kinetic control to the realm of thermodynamic control, in the case of the competitive formation of polymorphs dealt with in phase science, the winner usually takes all. Indeed, as the names "law of successive reactions" or "rule of stages" strongly imply, the formation of successive solid phases is probably more aptly viewed as a series of consecutive reactions in which each product or stage acts as a metastable reaction intermediate for the production of the next product in the sequence rather than as the competitive situation envisioned for the initial liquid or gas, and the same may be equally true of the $\text{NaOH}(\text{aq})\text{-Cl}_2(\text{g})$ reaction system discussed earlier.

It should also be noted that Ostwald's rule probably applies to situations other than just the competitive formation of crystalline polymorphs. Thus Walker suggested as early as 1899 that the initial formation of metastable plastic sulfur rather than crystalline rhombic sulfur upon rapidly cooling molten sulfur or the initial formation of oils and tars in organic chemistry prior to final crystallization of the desired product were all examples of Ostwald's rule in action (22), and the same is probably true of the initial formation of colloidal precipitates and their subsequent aging in the field of traditional wet chemical analysis (39).

Walker also suggested that Ostwald's rule was really a rule of least change—in other words, that the initial product corresponded to whichever phase deviated the least from the structure of the reactant phase (22). More recently Isaacs has suggested a molecular version of this idea in the field of organic chemistry based on the "principle of least motion," first suggested by Rice and Teller in 1938 (33, 40):

... those elementary reactions are favored which involve the least change in atomic positions and electronic configurations.

In short, the less structural and electronic rearrangement required, the lower the activation energy for the product in question, and the faster its rate of formation.

Last, but not least, the physical organic textbook by Klumpp has suggested that kinetic control automatically implies that the competitive reactions in question are irreversible, whereas thermodynamic control automatically implies that they are reversible (33). While the second of these statements is true by definition, the first statement is not (41), as demonstrated by the ability of many systems to switch from the domain of kinetic control to the domain of thermodynamic control as a function of reaction time and/or temperature and by our earlier analysis of figures 9, 11 and 12.

Indeed, the situation is even more complex than suggested by the above discussion since yet other possible potential energy surfaces are also conceivable, such as that given in Figure 13. For systems of this type both the kinetics and thermodynamics lead to an identical result and the potential energy surfaces are said to obey the so-called "noncrossing rule" (42). This situation is one of the fundamental, albeit often unarticulated, assumptions underlying the application of so-called linear free-energy correlations, as well as most of the approximate electronic reactivity indices much beloved of the modern-day organic chemist. This is especially true of those based on

the use of perturbation theory, though, as admitted by at least one leading theoretician, its validity appears to have been most often assumed after the fact rather than rigorously proven up front (42):

Such a procedure makes use of a rule known as the noncrossing rule, which states that for similar reactants the ratio of the energy necessary to reach any particular (but common) point on the respective reaction path curves is proportional to the ratio of the activation energies ... Although there is neither proof nor reason for such behavior, it has reasonably been verified experimentally and serves as a basis for most attempts to correlate chemical reactivity, particularly aromatic reactivity.

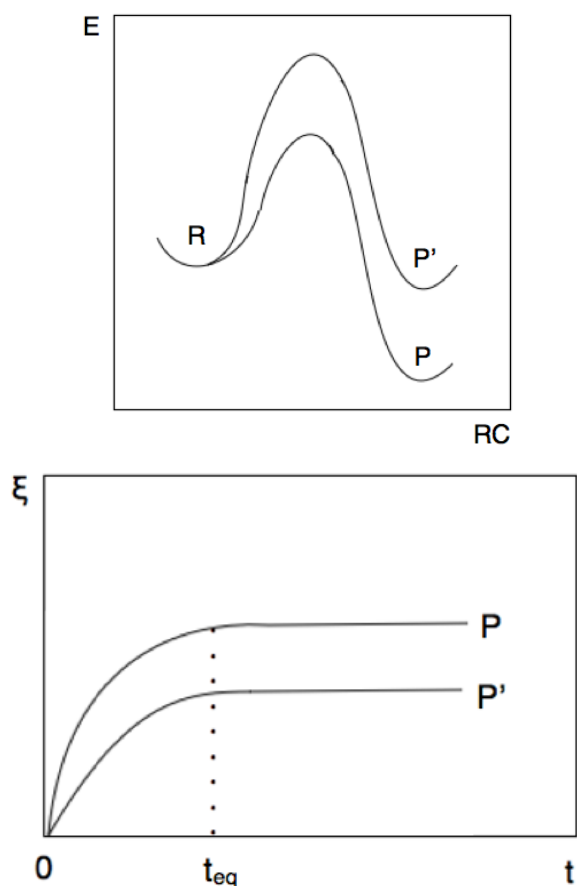


Figure 13. A potential energy plot and the corresponding extent of reaction - time plot for a competitive reaction obeying the noncrossing rule showing that kinetics and thermodynamics both predict the same dominant product (P).

The Ubiquity of Kinetic Metastability

Though first formulated by Gibbs in 1876, the phase rule did not begin to truly impact on chemistry until the

1890s (43). But once chemists realized that application of the rule held out the promise of definitively characterizing each known reaction system in the form of a summary phase diagram, their enthusiasm knew no bounds. Beginning with the work of the Dutch phase chemist, Bakhuis Roozeboom, in the period 1901-1910 (44), massive collections of experimentally measured phase diagrams began to appear in the literature, especially in those fields dealing with the high-temperature chemistry of metallic alloys and ceramics (45-47) and, with the introduction of the alternative predominance or Pourbaix equilibrium plots in the 1940s, in the field of room-temperature aqueous solution chemistry as well (48-50). Though these latter plots are not identical to phase diagrams, they also deal with equilibrium conditions, albeit with respect to reaction equilibria rather than phase equilibria.

Indeed, so enthusiastic was Ostwald about these developments that in 1907 he wrote a book entitled, in English translation, *The Fundamental Principles of Chemistry: An Introduction to All Textbooks of Chemistry*, in which he attempted to eliminate the atomic-molecular theory from chemistry and to instead operationally derive its most fundamental concepts on the basis of the phase rule and the use of experimentally measured phase diagrams (51). However, about a third of the way through the book, one gets the impression that Ostwald had begun to slowly realize that such an approach failed to capture many essential aspects of chemistry. As we have already seen, he was fully aware of the phenomenon of kinetic metastability in connection with the study of both phase transitions and homogenous reaction systems and dutifully mentioned both, as well as his *Stufenregel*, thus forcing himself to admit, as the book proceeded, the existence of an increasing number of exceptions to his program to base chemistry solely on the study of phase diagrams.

For example, someone who goes to the stock room to get a bottle of phosphorus will have a choice of either solid white (yellow) or amorphous red phosphorus, both of which are kinetically metastable relative to the thermodynamically stable black form and neither of which appear on the phase diagram for this element (52). Likewise, one may read an extensive literature on the role of ozone in protecting the environment from excessive UV radiation and its significance for the evolution of life on earth, or read of its properties in older descriptive inorganic textbooks, or even demonstrate its preparation for an introductory chemistry class, yet once again no trace of its existence will be found on the phase diagram for the element oxygen (52). Entire classes of chemical

compounds, such as the boron hydrides or the nitrogen oxides, also owe their existence to kinetic metastability and are missing from phase diagrams.

As noted by Ostwald near the end of his book, even more significant problems result when one looks at the phenomenon of isomerism and the chemistry of organic carbon compounds (51):

Cases of isomerism are found in very great numbers among carbon compounds, and this is because of two reasons: first, carbon compounds are very numerous and varied; second, they almost always exhibit an extremely small reaction velocity. This means that we are able to prepare and observe forms which could not be characterized as individual substances if other conditions held. The result of this condition has been that investigators have studied these individual substances, unstable of themselves, but easy of isolation because of their very small reaction velocities.

Thus in a few sentences Ostwald managed to dismiss the entire science of organic chemistry as the study of transient metastable reaction intermediates, and it must be admitted that this characterization is not far off the mark, since, with the possible exception of the aqueous phase chemistry of organic species with ionizable functional groups, very few phase studies are known for typical organic systems (53).

The point here is that both phase and Pourbaix diagrams are *equilibrium* diagrams and, as such, display only thermodynamically controlled reactivity. Though they sometimes attempt to incorporate information on kinetically controlled metastability in the form of dotted lines to indicate curves for supercooling or crosshatching to indicate regions of kinetic passivation due to surface precipitation, they, by and large, ignore the rich field of kinetically controlled reactivity with its many metastable compounds and allotropes—a world which gives chemistry much of its variety and fascination. While the information they contain on the equilibrium interactions within a chemical system is extremely valuable, they should never be mistaken for a complete picture of the system's known chemistry as unintentionally implied by the title of at least one such recent compilation (50).

Forgetting Once Again?

I first became interested in the subject of kinetic versus thermodynamic control of competitive chemical reactions when, as a young assistant professor at the Rochester Institute of Technology, I was assigned the task of developing a laboratory course in inorganic

synthesis. Among the preparations selected for use were several that involved the synthesis of various coordination isomers and it occurred to me that it would make an interesting exercise for the students to deduce which isomer was the thermodynamic product and which the kinetic product and how manipulation of the reaction conditions favored one over the other. Though this distinction lies at the very foundations of chemical theory and is one of the most fundamental questions that can be asked about a chemical reaction, I quickly discovered that the inorganic synthesis literature was all but silent on this issue. The various preparations given in typical lab manuals were presented as rote recipes to be followed, with little or no rationale as to how they were originally discovered or optimized or how they illustrated the application of the theoretical principles presumably learned in an earlier course on physical chemistry.

I had much the same experience several years later when writing a history of chemistry. In tracing the history of photochemistry, I discovered that much of the early theory in this field was based on supposed analogies with the process of electrolysis (54). In this latter process the applied electrical energy is being used to drive an otherwise thermodynamically unfavorable reaction uphill. Yet in many photochemical processes the applied light energy is obviously acting as a source of activation energy to initiate a thermodynamically favorable but otherwise kinetically inert reaction, such as that between dihydrogen and dichlorine gas. Just what was going on in the newer field of organic photochemistry was not so obvious, so I asked a colleague, who was an expert in the field, whether the majority of the reactions he worked with were thermodynamically allowed, but kinetically inert, and thus being photochemically activated, or whether they were thermodynamically unfavorable and were being photochemically driven uphill. The response was a blank look, as though the question made no sense, and an eventual admission that he had never thought about it one way or another as his focus was totally on the nature of the photochemically excited state and the details of the subsequent reaction mechanism.

Even more disturbing was a more recent incident involving the supposed preparation of $\text{HgF}_4(\text{g})$ using matrix isolation (55). I had previously written a paper pointing out that Zn, Cd and Hg were really main-block, rather than transition-block, elements since they never made use of either d-electrons or empty d-orbitals in their bonding (56), and the possible existence of mercury in a IV oxidation state obviously contradicted this conclusion. This was once again a case of competitive reactions, this

time involving the formation of HgF_2 versus HgF_4 rather than alternative isomers or polymorphs, and in my subsequent commentary I pointed out that the latter species, if it actually existed, must be a kinetically metastable reaction intermediate whose detection was made possible only by the fact that the extremely low temperature used (4°K) kinetically inhibited its dissociation (and isomerization when relevant) and the surrounding rare-gas matrix provided a diffusion barrier which kinetically inhibited molecular collisions among the various reactants and products and thus prevented polymerization (and disproportionation when relevant) (57). In this case inhibition of polymerization was key, as the supposed preparation theoretically depended on the favorable competitive formation of a monomeric $\text{HgF}_4(\text{g})$ molecule versus that of an isolated monomeric $\text{HgF}_2(\text{g})$ molecule and rapidly became unfavorable once the HgF_2 monomer was allowed to polymerize into the far more stable 8/4 infinite framework structure that HgF_2 normally adopts at all temperatures below 919°K .

All of this raised the further fundamental question of whether such transient species represented typical chemical behavior and whether they should be taken into account when classifying elements in the periodic table. However, when discussing the manuscript of the commentary with a colleague who specialized in matrix isolation, and in a subsequent e-mail correspondence with one of the coauthors of the original paper, both expressed great surprise that I had characterized the reported product as a transient kinetically metastable species and had interpreted the rare-gas matrix as a device for kinetically inhibiting polymerization. Though subsequent work failed to reproduce the reported species, the puzzlement that I encountered once again illustrated a widespread failure to explicitly think in terms of kinetic versus thermodynamic factors when dealing with chemical reactivity—a failure all the more disturbing as it involved specialists using a technique explicitly designed to optimize kinetic control.

Although admittedly anecdotal, such incidents would appear to bode ill for the prospect of making the concepts of kinetic versus thermodynamic control an inherent part of every chemist's thinking about competitive chemical reactions, whether they lead to alternative isomers, alternative polymorphs, or alternative oxidation states, and suggests that, once physical organic chemistry ceases to be a cutting-edge field and fades from the curriculum, its textbooks and lessons, like those of both affinity theory and phase science before it, will also fade from the chemical consciousness only to be rediscovered once again in some future context.

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2014 HIST Election Results

Congratulations to the winners of 2014 HIST division elections.

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- Secretary/Treasurer (Term 2015-2016): Vera Mainz
- Councilor (Term 2015-2017): Mary Virginia Orna
- Alternate Councilor (Term 2015-2017): Art Greenberg

As 2014 comes to an end, Ned Heindel ends his term as HIST Chair, replacing E. Thomas Strom in the Past Chair seat on the Executive Committee. Gary Patterson succeeds Heindel as Chair, and Brashear succeeds Patterson as Chair-Elect.

ON THE FIRST LAW OF THERMODYNAMICS AND THE CONTRIBUTION OF JULIUS ROBERT MAYER: NEW TRANSLATION AND CONSIDERATION OF A REJECTED MANUSCRIPT

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Introduction

The first law of thermodynamics is a cornerstone of the chemical sciences. Its investigation in the nineteenth century augured and helped propel the industrial revolution. The core idea is elementary: regardless of the process and composition of a system and surroundings, energy is conserved at every instant. In simplest terms,

$$\Delta E_{\text{total}} = \Delta E_{\text{system}} + \Delta E_{\text{surroundings}} = 0$$

This is an exact law of nature—hence the equal signs in the above and with zero violations. A particularly insightful discussion of the first law has been presented by Denbigh (1).

It is a truism that nature's laws are established via experiments conducted by trained scientists. Thus in the nineteenth century, several individuals—Joule, Helmholtz, Thompson (Rumford), and Colding—focused on energy transformations in new quantitative depth and breadth. Yet truisms meet exceptions: the non-scientist Julius Robert Mayer is recognized *along with* the luminaries for proposing the first law concepts. Mayer's life and works have consequently warranted the scholarship of numerous science historians over the years. We call particular attention to the research of Caneva (2, 3), Gumpert (4), Steffens (5), Lindsay (6), and Truesdell (7). Four of these scholars have written monographs about

Mayer. Truesdell has presented a captivating view of nineteenth century thermodynamics as a whole.

A person's professional oeuvre is embodied in publications, notebooks, and conference presentations. But there is another interesting, far-less-examined category, namely *rejected* manuscripts. These report advances that are regarded with confidence by their authors to be stand-alone contributions to a field. Editors and reviewers pronounce otherwise whereupon the manuscript must find another venue for dissemination. In some cases, the report languishes outright, rarely (if ever) to see the light of day.

J. R. Mayer's journey through thermodynamics includes the above scenario. His rejected paper "Über die quantitative und qualitative Bestimmung der Kräfte" presented a highly non-canonical probing of the first law in 1841. Mayer's viewpoint was not grounded upon apparatus, procedure, and data—tools of the scientific trade. Quite the contrary: he appealed to natural philosophy, the rudiments of which he acquired at a theological institute equivalent to modern-day high school. Mayer's professional training was in medicine and surgery and his university years in Tübingen did not allow time for philosophy. Yet his pre-medical grounding as a teenager included principles developed by Aristotle, Kant, and Schelling. Here forces are viewed as central to all phenomena. Matter is that which can be moved by forces and

nature is indestructible by virtue of its forces. In effect, forces are primary.

Mayer's rejected handwritten manuscript was "re-discovered" in the *Poggendorff* Nachlass (i.e., that which remains in residual files) in 1877 and published in facsimile format by F. Zöllner in 1881 (8). The publication appeared three years after Mayer's death and forty years post submission of the manuscript to Poggendorf's *Annals of Physics and Chemistry*. While the original paper was lost in succeeding decades, the facsimile survives and has been discussed in several places (9). A transcription was published in a volume of Mayer's letters and other short works (10). A translation and brief commentary appear in Lindsay's book (6).

The present authors give renewed attention to Mayer's *first* albeit rejected work. We obtained a copy courtesy of the Stadt archives in Heilbronn, Germany. In so doing, we present an original, close translation of Mayer's words and focus on the philosophical and thermodynamic subtleties. We find the dismissed ideas to reflect several nuances of thermodynamics along with their universal scope. This was in spite of Mayer side-stepping manual labor and mathematical sophistication to bolster his arguments. It is just as clear that Mayer was writing independently of scientific ferment in the 1840s.

Mayer and Manuscripts—Accepted and Rejected

The majority of scholarship regarding Mayer has been initiated by his 1842 *accepted* paper: "Bermerkungen über die Kräfte der unbelebten Natur" (11). This is traditionally referred to as Mayer's *first* paper as it was indeed his inaugural publication. Joule, in his notebooks, included crude translations of this work and eyebrow-raising comments (penned in the margins) such as "Stupid! Does not everyone know this?" and "This is all old, and due to Davy and Rumford" (5). Some twenty years later, "Bermerkungen über die Kräfte" sparked a controversy. While presenting a lecture, Tyndall bestowed credit to *both* Mayer and Joule for establishing the first law of thermodynamics. Then over a several-year period, various parties responded to such sentiment with supporting arguments and denunciations, often acrimonious (7). All the while, Joule and Mayer *each* claimed priority of the first law discovery. Not incidentally, Helmholtz made references to Mayer as one of the founders of the principle of energy conservation. Helmholtz's 1854 lecture in Königsberg entitled "The Interaction of Natural Forces,"

specifically acknowledged Mayer's priority of discovery over Joule, Colding, and himself (12).

Obscured in the vitriol and occasional graciousness were Mayer's *first* words aimed at a journal audience. They are dated June 16, 1841, and were penned following Mayer's return from a sea voyage as ship's physician. A translation of the paper "On the Quantitative and Qualitative Aspect of Forces" follows (13). We have stayed as close as possible to the German lest we distort Mayer's intentions. In only a few places have we contemporized individual words and collective syntax. In particular, *Bestimmung* is most often translated as *determination*. We believe it best rendered as *aspect* or even *diagnosis* (14). Mayer was writing not just as an amateur philosopher, but also as a physician and surgeon.

The heading on the rejected manuscript is:

Über die quantitative und qualitative Bestimmung der Kräfte

Von J. R. Mayer, Dr. Med. & Chir., prakt. Arzt zu Heilbronn

This translates to "On the Quantitative and Qualitative Aspects of Forces." The author duly notes his occupation as a physician and surgeon in Heilbronn.

The task of natural science is to relate the phenomena in the inanimate as well as the living world according to their causes and effects. All phenomena or processes are based on the fact that substances, objects, are changing the relationship in which they stand to one another. According to the law of the logical reasoning, we assume that nothing is happening without a cause, and one such cause we call force. We are getting to phenomena, following the causal connection upward, of which the causes are not accessible to our senses, but only can be abstracted from their effects, thus we call these forces, in the narrower sense, abstract forces.

This is Mayer's take on natural science. In the philosophy of Kant and Schelling, all knowledge must be justified (15, 16). The high style is consistent with the times.

— All phenomena can be derived from one primordial force, which acts in the sense to cancel the existing differences, so that it combines all existence to one homogeneous mass in a mathematical point.

Mayer cites two notions in philosophical vogue in the nineteenth century. He reflects that there exists a force in the universe that is overriding. This force is the source of all—not just selected—phenomena. He follows this by declaring that the primordial force causes all systems to tend toward a most unusual state of equilibrium. By no

means is Mayer speaking solely his own mind. Schelling viewed all in the world as unity arising from a single primordial source. All natural manifestations stem from the source and differ only by their particular mode of motion. In Schelling's (and apparently Mayer's) view, it is the *conflict* of forces that discloses the nature of chemical and physical phenomena (17).

—Two objects, that are in a state of some definite difference, could remain in a state of rest after having cancelled that difference, if the forces imparted to them by the cancellation of the difference, could cease to exist; but, since these are deemed as being indestructible, thus they are still existing forces and act as causes of relationship changes that restore the continuance of a difference. Thus the principle that existing forces, just like matter, are quantitatively unchangeable ensures us conceptually of the continuance of the differences and with that of the material world. Both sciences, the one that concerns itself with the kind of existence of matter (Chemistry) as well as that which concerns itself with the kind of existence of forces (Physics), have to consider the quantity of their object as indestructible and only the quality of the same as changeable.

The last sentence is pivotal—that the *quantity* of an object is indestructible; only its *quality* can be altered. In no uncertain terms, Mayer is declaring that the mass and forces within a system are conserved. We note that by 1840, the works of Lavoisier on mass conservation had been well disseminated (18). Mayer was an astute reader of this literature prior to writing his thermodynamics papers (12).

Two things, A and B, on whose relationship act change-producing forces, present principally the following situations: 1) they are either spatially separated, and then motion is the change of their relationship, or 2) they are not, and then changes in their relationship are related to chemical combination and separation and on special conditions, that occur at the contact of the bodies and produce electrical phenomena. At the moment, we speak only of the force that produces the change in the spatial relationships of the bodies, that is, of the moving force.

If we place two objects in an isolated universe and impart a given difference to one another, both would move in a straight direction toward one another; the ultimate cause of the forces, or the cause, which manifests itself by the compensation of the existing difference, imparts to both bodies the moving force by whose consequence or appearance we see the motion occurring. The motion, which is existing at any moment, we determine quantitatively by the product of the mass times the velocity. Since the causes always relate themselves to the effects, thus the moving

forces relate themselves to the motions, thus this product MC also will supply an exact contribution to the moving force V ; consequently, we set $V = MC$.

Mayer uses V , M , and C to denote force, mass, and velocity, respectively. He quantifies the motion of a body as $V = MC$. Mayer apparently possessed fragmentary knowledge of motion laws.

Since a given definite amount of $V = MC$ can be considered as determining the size of the movement, thus it is now a question of the determination of how this quantity of force expresses itself, or in how this motion proceeds, and this we define by the name *Quality* of motion. It includes

- (a) the energy of the motion or its relationship between its Intensity and Extensity. Important for quality is n in the expression $(M/n) \cdot nC$, in which n can express any whole and any fractional number,
- (b) provided we consider only diametrically opposed directions, the direction of the motion can be completely expressed by the simple signs $+$ and $-$, in addition it is necessary to draw the projection by lines by whose length at the same time measure the quantity of the motion.

Mayer addresses the *quality* of motion. While he speaks imprecisely about energy, momentum, and forces, he sets the stage for assessing heat as motional in nature. Heat must have a quality that is fundamentally different from other forms of energy. Under heading (a), Mayer also discriminates intensive and extensive properties. This discrimination is a central facet of thermodynamics (19). Under heading (b), Mayer states the obvious: for motion in one dimension, the direction can be assessed simply via plus and minus signs. Mayer punctuates the idea via two diagrams in the manuscript. His “+” refers to rightward motion of a body; “-” applies to leftward motion. The lengths of straight lines allied with each type of motion scale with the magnitudes.

Let's consider A and B , two objects, that are spatially separated and to which—disregarding gravitation—the moving forces v and v' are imparted; their respective velocities are c and c' , thus $Ac = v$ and $Bc' = v'$, thus the quantity of the moving forces is invariably determined. Let $A = B$ and $v = v'$ and thus the total quantity of the moving forces is $Q = 2Ac$. —For the determination of the Quality of $2Ac$, we choose first of all the most simple case that A and B are moving in a direction straight toward one another; then $+Ac = -Bc$; the sign for the combined objects, A and B , is neither $+$ nor $-$, but it is the sign 0 , since A and B taken together will have neither motion toward one or the other; the movement $2Ac$ must thus proceed so that for every $+$ motion there corresponds an equal motion in the opposed direction; therefore, these $2Ac$

could neither become + nor –, but [it] they must be expressed by the sign 0; it is therefore clear, what is to be understood by the expression $0 \cdot 2Ac$; it is evident, that in no way is it synonymous with the numeral 0 and that the $2Ac$ package of force does not lose from its value by the prefaced qualitative sign 0; $2Ac$ is not decreasing in its amount owing to the previously set qualitative sign 0; $2Ac$ is the measure of the differentiation from the sign 0.

Mayer discards gravitational effects, as has become customary for thermodynamic systems. He focuses on the simple case of two objects possessing equal-magnitude, but opposite momenta. The result is that the combined scalar magnitude is *twice* that of either object motion taken individually. Mayer elects a roundabout way of saying that the vector sum of the motion quantities is zero. In Mayer's notation, the vector sum of the momenta is indicated by the "sign" zero. $2Ac$ represents the scalar sum of the vector magnitudes of the two objects in question. Curiously, Mayer constructs an ordered pair $(0, 2Ac)$ which he allies with a conserved quantity of motion. The confusion notwithstanding, emphasis should be placed on the insight that the "package of force does not lose from its value... ."

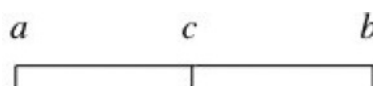
For the determination of $0 \cdot 2Ac$ two opposing motions can suffice; however, it is possible for motions to occur from many, indeed from all directions; it is only necessary, that to each movement corresponds an opposing equivalent one; thus from the contact point of *A* and *B*, considered as a midpoint, all directional-radial, oscillating, wave form motions can occur. As far as the further qualitative determination of the energy of the movement is concerned, it depends, as mentioned, on the determination of *n* in $0(2A/n) \cdot nc$; the size of *n*, however, depends on the physical nature of the concerned object and its surroundings, and above all else on the efficiency of the substances for the moving force, i.e., the elasticity. In the case of perfect elasticity of *A* and *B*, then $n = 1$, $+Ac$ very simply is turned around into $-Ac$, $-Bc$ into $+Bc$: in the same measure when the elasticity is decreasing in respect to completeness, we see less movement generated, and in complete inelasticity, we see a complete cessation of motion: in the measure for inelasticity, by entirely stopping, we see less motion occurring and in the case of more complete inelasticity the motion discontinued entirely.

A part of the moving force $2Ac$ or the total of the latter, under such circumstances actually are removed from observation; this quantity consisting of + and –, we call transformed.

According to the assumption of the unchangeability of the quantity of forces, the quantity transformed is equal to the original motion occurring minus any

force remaining; at complete inelasticity of *A* and *B* the transformed force is $= 2Ac$.

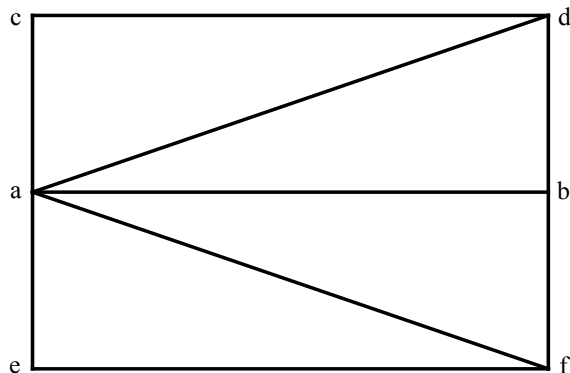
Mayer considers collisions of objects and the contrast between elastic and inelastic ones. For inelastic, the magnitude of the combined momenta *decreases*, sometimes even to zero. Irrespective of the elasticity, the vector sum holds at zero. The second term in Mayer's ordered pair is influenced by the state of elasticity and so is varying from $2Ac$ to 0. Mayer recognizes that the difference must be accounted for—indeed transformed—into something else—perhaps heat, as we will see below. Of course, we know that the energy, not the scalar sum of momenta, is the quantity that is conserved. The mathematics of collisions was taken up in detail three decades later by Ludwig Boltzmann. Boltzmann includes brief commentary on Mayer's works in his *Lectures on Gas Theory* (20).



—If we now describe the motion of *A* by ac , and that of *B* by an equal bc , thus ab becomes the measure of the transformed [force] $= 2Ac$. The point *c*, that we call the null point, has its position in the middle, when it has been established by equally large opposed forces; it can, however, also be thought the zero point, so far as it is considered a fixed point, it could be situated at the end of the line. If a motion, ab , is brought to a stop at the fixed point *b*, again thus $ab = 2Ac$, the amount of the transformed [forces], so that the result in both cases is equal.

The motions ac and bc can only then completely neutralize themselves when the angle $acb = 2R$. This result is in the same way less complete as the angle $acb < 2R$. In the case the angle $acb = 0$ the motion continues in its total value, thus the neutralized part becomes also $= 0$. If two motions meeting at an angle and combining themselves into a single motion, the direction of the value of the resulting motion will be given by the parallelogram of the forces; the neutralized part will thus become, as above indicated, the initially existing force minus the remaining, thus equal to the sum of the combined, minus the resulting. It is understood that the creation of a neutralized force presupposes the existence of real motion, thus no neutralized component is attributed to statics.

We have used the word "neutralize" to encapsulate "to make ineffective by an opposite force." Mayer does not define *R*; however, it clearly refers to a right angle. He does, however, include two diagrams, which are redrawn here.



If we set in the parallelogram $abdc$, ad positive, then $ab + ac = ad +$ the neutralized motion, N , $ab + ae = af + N$, or since $ae = -ac$, $ab - ac = af + N$. By $ab - ac$ is obviously understood, that to the motion ab given magnitude and direction, is added another of the magnitude ac , but of the opposing direction; thus it is concluded that the contributors $ab + ac$ and $ab - ac$ give the same sum, thus will also $ad + N = af + N$. If we would wish, however, instead of adding to ab the motion ae , we subtract from it ac which is equally large but of opposite direction, thus obviously the remainder will be smaller by $2ac$, or by $0\ 2ac$ than the previous sum; if one will express this difference by zero, thus one obtains by subtraction of ac and by addition of ae exactly the same result; the same applies also for $ad - ac = ab + N$. Without presenting further examples, we will only briefly indicate, that one of the usual applications of the parallelogram in dynamics always obtains results that are either too small or too large with respect to the neutralized motion. However, the results are completely correct concerning the kind and manner of the actual motion. The difference regarding the neutralized motion lies in the calculation then always equal to zero. As the case requires, opposite motion becomes zero, or, is allowed to proceed from zero, originating from opposite-direction motion.

Again, we recognize that the quantity Meyer treats is momentum rather than energy. In order to correctly add momenta, he must apply vector addition by the parallelogram law which leads to complications. The basis of his misconception is that for non-parallel vectors, vector addition *differs* from scalar addition. The magnitude of the resultant vector is always *less than* of the scalar sum of the magnitudes of the original vectors. The representation $0\ 2Ac$ is a combination of two different quantities. In the first position occupied by the 0 is a vector sum of the momenta of the moving objects. The position occupied by $2Ac$ is the sum of the scalar magnitudes of the momenta of the moving objects.

Since indeed in our physical apparatuses forces can elude observation but, never can something be obtained which would be developed from zero, thus are likewise cases suited for experimentation in which the neutralized motion is left out, never, however, such, in which the formation of one has been proposed from zero; especially thus may ab and ac be combined to an ad , never, however, from an ad can two motions result, which have the magnitude of ab and ac , but they could be in any directions they wish.

Let it be now permitted to us, from the above to deduce several conclusions for the natural science. —The neutralized $0\ 2MC$ is, in as much as the motion takes place not actually toward the opposing directions, the expression for heat. Motion, heat, and as we later intend to develop, electricity are phenomena which can be traced back to *some* force, and can be measured reciprocally and converted one to another according to definite laws. Motion converts into heat, by being neutralized by means of an opposing motion or by means of a fixed point, the heat produced is proportional to the motion that has disappeared. The heat on the other hand converts into motion in such a way that it expands the bodies; it causes, according to its general formula $0\ 2MC$, with $+MC$ or $-MC$, according to the particular case, opposing but all directional (radial) movement, the heated body itself remains at rest, therefore, it is designated the qualitative sign 0 : A particular class, the transformation of simple motion to heat, creates the waves and the oscillating motions; in as much as they are radial, they are assigned the sign 0 ; in respect to heat they differ, however, in this way, so that with the latter, the motions keep their form of motion all the time; the magnitude of these motions can likewise also to be defined by $2MC$; based on differences in energies, they produce different results. In the formula, $(M/n)\ n\ C$, as given above, n , is the energy of the motion; if $n = \infty$ (at least close to ∞ , may we be allowed to use this expression to make it short), thus we obtain the kind of motion, which portrays itself as light or as radiant heat. Light thus receives the movement: $(0\ 2\ M / \infty) \cdot (\infty\ C)$. Light forms heat when the motion converts to rest; from heat, light emerges when the accumulated neutralized motion again assumes the form of motion.

Mayer is overreaching by tying light, oscillations, and heat via simplistic reasoning—he uses symbols $(M/n)(nC)$ for light—perhaps for sound as well. Even so, he recognizes the universality of energy imbedded in nature's forces. In the 1840s, light was well known to travel at a great (albeit unmeasured) velocity and to carry no mass.

If we connect an object, P , by an imaginary radius vector to a fixed point c , and produce through the P

imparted motion MC , the peripheral motion, then MC splits into two motions, of which the first has the direction of the periphery, but the other, however, the direction $-Pc$; due to the fixed point c , the latter is constantly diminished, neutralized, thus one can see that MC imparted to P in c step by step becomes 0 MC , hence the motion of P thus is constantly decreasing. In the systems of the heavenly bodies gravitation represents the imaginary radius vector; instead of subtracting from the motion MC a motion in the direction $-Pc$ there will be added one in the direction $+Pc$ and through the forces, which are moving according to the combined laws of the statics and dynamics, are obtained not only the permanent movement of the celestial body P , but also by c for each revolution a measurable amount of motion neutralized. Expressed in another way it says this: in the same amount as the peripheral parts behave like they are falling to the center, the center falls toward the periphery.

Mayer abruptly takes up planetary motion. Because of his confusion with the "Neutralized," he had to invent a motion for his fixed point (due to gravity) in order to eliminate the "Neutralized." In Mayer's thinking, the planets are thereby able to revolve forever about the sun.

In the star systems there is, therefore, a permanent development of a force, which for us is an insoluble problem, i.e., the changing of 0 to $+MC - MC$ that has been solved by nature; the fruit thereof is the most wonderful part of the material world, the perpetual source of light,

In concluding remarks, Mayer mentions the eternal shining of the sun. He has no explanation of the source of the sun's energy. This problem regarding the sun's energy source had long troubled scientists and philosophers. Mayer reiterates the universality of energy and its transformative properties.

* — To be continued.

* The author puts forth the above principles, which in part form the basis of his concept of nature, intentionally in the shortest possible way. Truth requires for recognition not many words, and to desire to puff up errors as true is a vain attempt.

These words close the manuscript. Mayer indicates there is more to be said. His follow-up was a second manuscript that was accepted and published by *Liebig's Annalen* in 1842 (11).

Discussion

Early in his career, Julius Robert Mayer, although well educated, was not a member of the science community. By all accounts, he was confident in his abilities

and openly sought recognition. These traits may have rendered him ill-suited to the Lutheran ministry, his original career path. Mayer instead became a physician, surgeon, and one-time ocean voyager. By his imagination and interests in fundamental concepts, he can be described as a creative thinker and *de facto* theoretician. It is noted that in late life, Mayer became sufficiently well known to share the podium at meetings with luminaries such as Helmholtz. Helmholtz was not alone in his acknowledgement of Mayer (6, 12). In particular, Mayer merited the praise of Tyndall which was to spark the controversy regarding the discovery of the first law of thermodynamics (7). The reader is directed to books by Lindley (21) and by Miller (22) for a clear-lens views of the priority controversy, in addition to the Mayer scholarship already cited (2-7). In effect, the star of Mayer's scientific reputation rose until his death in 1878, although he never lacked for critics. His life did not lack for tragedy as well: witness the death of children and attempted suicide. Curiously, Mayer is typically cited in the literature as *both* a physicist and physician. Thus, bearing in mind the philosophical content of his pre-medical studies, it is not surprising that he treated his early concept of forces from the perspective of a theorist rather than that of the physicist-experimentalist.

From a philosophic perspective, it is standard procedure to posit ideas in the absence of experimental proof. Mayer, in his rejected manuscript, buttressed a hypothesis concerning forces by the method of philosophic argument. In concept, he crafted an independent and, for significant parts, correct presentation. However, he undercut his efforts by a hurried and sketchy elaboration. In hindsight, we can see that he focused on the wrong measure of motion (momentum rather than energy), and incorrectly applied scalar and vector addition. Such errors may not surprise as vectors and scalars were scattered topics prior to Maxwell's contributions to electromagnetic theory (23). In addition, Mayer failed to appreciate the angular momentum of central force motion in his digression on planetary motion. Mayer's work was dismissed without comment by an established science journal. Yet we point out that he was neither alone nor the first to embrace science and philosophy simultaneously. Oersted in 1820 attributed electromagnetism properties to his metaphysical belief in the unity of all natural forces (24).

It should also be noted that Mayer committed several novice mistakes in publication strategy. He submitted a theoretical and speculative paper. He offered no experimental data and aimed at a medium distinguished

for reports of rigorous experimentation and quantitative analysis. In addition, Mayer made the point to the editor that he (Mayer) considered the concept so crystal clear that he did not need to do much explaining. He purposefully wrote in a condensed style, the run-on sentences notwithstanding. He also assumed that the journal readership would find the mathematical treatments, diagrams, and physical significance wholly self-evident. Additionally, Mayer gratuitously informed the editor that only in papers that possibly were in error did the author need to use extensive discussion. Finally, he ended his paper with the terse comment “to be continued.” Mayer had a favorable opinion of his thoughts put to paper.

But there is arguable reason for the opinion as debated over the years. Mayer recognized that he was treating a broad principle of nature, which cut across *both* the animate and the inanimate world. This was revolutionary in some respects as the animate (and especially human) world was widely thought to be exempt from inanimate-guiding principles. Moreover, he initiated discussion via a *model*—an elementary construct grounded upon an operational definition of natural science and, sentences later, motion in one dimension. Then Mayer asserted that all phenomena are derived from one primordial force which pushes all systems toward equilibrium. Next he pointed out that forces are held to be indestructible in accord with theological and philosophical foundations. After that, Mayer noted that the substance of chemistry (matter) was indestructible and that the substance of physics (force), just like matter, was also indestructible. As the lynchpin, he reckoned that the material world could be reasoned to be indestructible. This final observation completed the model. Mayer had arrived at the conservation laws for material and the *forces* behind *all* motion. We understand these entities today to underpin the first law of thermodynamics. Also, he gave a practical definition of heat in attempting to explain the conservation of motion and its transformation into heat. On this account, Mayer may be credited with helping to overthrow the Caloric theory of heat. His perspective was not experimental, but by *cause* and *effect* reasoning—*causa aequat effectum*. If a system contained and/or transferred heat, there *had* to have been causes underpinned by forces. This was non-conformist at the time. As of the early nineteenth century, heat was viewed as a *cause* of phenomena: it predicated fires, summertime discomfort, winter survival and so forth. Mayer contemplated matters in quite the opposite direction.

Mayer attempted to support his construction via mechanical examples. In each case, he developed an

argument that momentum conservation was valid and indeed absolute. He ended his paper by positing that the orbital mechanics of the heavenly bodies adhered to his model; however, the light energy from the stars was insufficiently understood to allow interpretation. In concept, Mayer’s support of his model by mechanics was sound. However, his shaky command of physics resulted in glaring errors. These diminished his credibility with science contemporaries and certainly with the journal editors. However, Mayer’s problems with theoretical exposition on conservation principles in no way diminished the veracity of his central theme. Mayer uses the word *Energie* in his rejected manuscript in three places, although it is not evident that the word has the same meaning as it carries today. In his follow-up work appearing in *Liebig’s Annalen*, the paper often credited for the concept of conservation of energy, he curiously does not write the word *Energie* anywhere.

Julius Robert Mayer was a creative thinker—and dedicated. During the voyage to the East Indies, he was overwhelmed by *his* recognition of the law of conserved forces. While in port, he declined the pleasures afforded by the shore and chose to remain on board the ship. Mayer was *that* obsessed with contemplation of a new concept. We close with Tyndall’s appraisal of Mayer in an 1891 letter written to Jacob Johann Weyrauch (25):

No greater genius than Robert Mayer has appeared in our century. Some men who now overshadow him will be undoubtedly placed beneath him in the future history of science.

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Bruno Jaselskis is Professor Emeritus of Chemistry at Loyola University Chicago. He was born in Lithuania. Following World War II, he worked in Germany for UNRRA—the United Nations Relief and Rehabilitation Administration—and the World YMCA. He immigrated to the United States in 1949 and proceeded to earn a B.S. degree in chemistry at Union College of Schenectady, New York. This was followed by work for the masters and doctoral chemistry degrees at Iowa State University. Professor Jaselskis subsequently joined the chemistry faculty as a lecturer at the University of Michigan. After five years, he moved to Chicago to become an Assistant Professor at Loyola University in 1962. Over the years, his research has focused on analytical chemistry, the chemistry of noble gases, and the historical development of the chemical sciences.

Carl E. Moore passed away in early 2012 as Emeritus Professor of Chemistry at Loyola University Chicago. He had been a Loyola faculty member since 1952. Professor Moore was born in Frankfort, Kentucky, and received a B.S. degree in chemistry from Eastern Kentucky State Teachers College in 1939. This was followed by an M.S. degree in chemistry from the University of Louisville in 1947. He matriculated at the Ohio State University following WWII and completed work for the doctoral chemistry degree in 1952. He joined the Loyola University faculty immediately thereafter. His research and teaching of six decades concentrated on analytical chemistry and the philosophy of science. During the 1970s, Professor Moore completed a six-year tour of duty as department chair at Loyola Chicago.

Alfred von Smolinski passed away in 2009; at the time he was Professor Emeritus. He was born in Cernauti, Romania, in 1919. He pursued chemistry studies for three years at the University of Cernauti. He then transferred to the University of Bucharest for his final undergraduate year and received the diploma in chemistry. In 1942, he moved to Germany and was employed in the chemical industry. In 1955 he immigrated to Chicago and received the M.S. and Ph.D. degrees from Loyola University Chicago. His research was supervised by Professor Carl E. Moore. Following the years at Loyola, Professor Smolinski taught chemistry at Youngstown State University and at the University of Illinois Chicago in the Department of Medicinal Chemistry.

Daniel J. Graham is Professor of Chemistry at Loyola University Chicago. He was born and raised in San Francisco, California. He completed a B.S. degree with honors at Stanford University in 1976. This was followed by doctoral studies in physical chemistry at Washington University, St. Louis. He carried out postdoctoral work in molecular spectroscopy at Boston University. This was followed by a chemistry faculty position at West Virginia University. Professor Graham moved to Chicago in 1987 to join the Chemistry Department of Loyola University. His research focuses on thermodynamics and information theory applied to organic compounds.

Albert Claus is Professor Emeritus of Physics at Loyola University Chicago. He was born and raised in Chicago and earned his undergraduate degree at Northwestern University in Evanston, Illinois. He proceeded to doctoral studies in physical chemistry at the California Institute of Technology in Pasadena, California. Professor Claus's graduate research in x-ray crystallography was supervised by Linus Pauling. Following his Pasadena years, Professor Claus became a chemistry faculty member at the University of Alaska in Anchorage, Alaska. After two years, he moved to Chicago and soon joined the Physics Department of Loyola University in 1962.

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Organized by: José Ramón Bertomeu Sánchez and Ximo Guillem-Llobat

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- Nathalie Jas (RiTME Research Unit, INRA), Pesticides. How and why regulating "unruly technologies"? An historical analysis.
- Gerald Markowitz (John Jay College and Graduate Center, CUNY), Lead Wars: The Politics of Science and the Fate of Children

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EARLY PRACTICAL CHEMISTRY AT BRITISH PRIVATE GIRLS' SCHOOLS

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Abstract

Contrary to most accounts, experimental chemistry was a key part of the education of girls at private British girls' schools in the late 19th and early 20th centuries. Here we report detailed evidence on the teaching of practical chemistry on the basis of archival searches at many of these schools. In particular, we have found photographic evidence of numerous school chemistry laboratories and we have contextualized the laboratory experience of the times.

Introduction

In the early part of the 20th century, Angela Brazil (1868-1947) wrote a range of fictional stories of life at private British girls' schools (1). To indicate that the story was set at a forward-looking school, Brazil included in the saga the presence of a chemistry laboratory. For example, in the 1906 novel, *The Fortunes of Philippa*, reference is made to: "... we had chemistry classes in a well-fitted laboratory ..." (2). In *The School by the Sea* (1914), the school, Dower House, is a former nunnery founded in the 14th century. The headmistress, Miss Birks, muses that "Could the Grey Nuns have but returned and taken a peep into the well-equipped little chemical laboratory, they would probably have fancied themselves in the chamber of a wizard in league with the fiends of darkness, and have crossed themselves in

pious fear at the sight of the bottles and retorts; ..." (3). To have entered the realms of fiction-writing for girls, it would seem that chemistry was considered an expected part of a girl's education at such schools.

In our previous work, we showed that private (called "independent" in Britain) girls' schools were at the forefront of chemistry education in Britain in the late 19th and early 20th centuries (4). Our research went against the common perception, not only about the introduction of chemistry into British schools, but particularly the practical aspects. For example, in an account "The Teaching of Chemistry and its Development" the first practical chemistry was said to have been performed at the (boys') City of London School in 1847, while the first school to offer practical chemistry in a laboratory setting was claimed to be the (boys') Manchester Grammar School in 1868 (5). No mention is made anywhere of the teaching of chemistry at girls' schools. Even a more recent comprehensive study on the history of science education in Britain relegated the teaching of science to girls to a single chapter out of a total of eight chapters. In that chapter, the author commented on the inadequacy of, and often lack of, girls' school chemistry laboratories until the 1960s (6). Also of note, all photos of school laboratories were those of boys' schools. We have therefore further researched the issue, accessing the archives of 54 independent (private) girls' schools and uncovering additional documentation, and, in particular, photographic evidence of some of the school chemistry laboratories and of the student experiments.

Practical Chemistry at Girls' Schools

The earliest record we have discovered so far of teaching chemistry at a girls' school is that of the Newington Academy for Girls, a Quaker school in Stoke Newington, London (7). Opened in 1824, one of its founders and teachers was the Quaker scientist, William Allen (1770-1843). From the beginning, chemistry was taught and the chemistry demonstrations would probably have been the first at any school in Britain. One of the students, Louisa Stewart, later recalled: "William Allen gave the girls lessons in his own house in chemistry..." (8). In her memoirs, the social reformer Sophia Elizabeth de Morgan (1809-1892) mentioned meeting Allen sometime in the mid-to-late 1820s: "... I made the acquaintance of William Allen, who kindly allowed me to attend the lectures on chemistry which he gave, with experiments, to a class of young girls." (9). Unfortunately, the school closed in 1838.

Quaker girls' schools seem to have been at the forefront of introducing chemistry, another example being the Mount School for Girls, York, where practical chemistry was demonstrated by an Edward Grubb in the 1860s. As the school historians, Winifred Sturge and Theodora Clark commented: "To his lectures on chemistry his audience came in a mood of prophetic sympathy, awaiting the experiment: "Will it? Won't it?" It generally wouldn't! Why should it? For before the laboratory was built in 1884 there was no scientific equipment worth the name" (10).

Though the Quaker schools led the way, other independent girls' schools soon followed. Princess Helena's College (founded originally in 1820 as the "Adult Orphan Asylum" to train governesses), then located at Ealing in west London, began offering chemistry in 1890: "Mr. G. S. Newth, of South Kensington Science Department, gives the Chemistry Lectures, and makes them most interesting to his class by his numerous and beautiful experiments" (11). Newth, demonstrator and lecturer at the Royal College of Science (later Imperial College), was a prolific writer of chemistry texts, including *Chemical Lecture Experiments* (12).

The impetus for introducing chemistry was the opening of London University to women in 1878 (13), for, at the time, grade-school chemistry was a necessary prerequisite for admission. This point was made explicitly by the Headmistress of St. Leonard's School, St. Andrew's, Scotland, Miss Dove, to the Administrative Council of the School in 1880 (14):

A letter was read from Miss Dove regarding the necessity of procuring certain chemicals and chemical apparatus with a view to the preparation of pupils for the examination of the London University. It was agreed that a sum not to exceed 15 pounds might be expended for this purpose.

It is clear from subsequent Minutes that Miss Dove was in charge of decision-making (15):

The account for the chemical apparatus etc. obtained by Miss Dove amounting to £22.15.10 was laid upon the table. It was explained that every economy had been used in the purchase of the necessary materials and in the circumstances it was agreed that the full amount should be paid by the Council, although exceeding the sum formerly agreed upon.

In England, the leading girls' school for experimental chemistry was the North London Collegiate School (NLCS) (16). From its inception in 1850, the founder, Frances Mary Buss had included chemistry in the curriculum, her father, Robert Buss teaching the subject by means of demonstrations with memorable "smells and explosions" (17). Moving the school to a new building in 1885 enabled her to incorporate a custom-designed chemistry laboratory in which the girls could do hands-on experiments themselves (Figure 1). Of particular note are the individual vents over the lab benches. The laboratory was designed by the renowned architect of technical and college buildings, Edward Cookworthy Robins, the original plan for the NLCS laboratory (Figure 2) being included in his monograph *Technical School and College Building* (18).

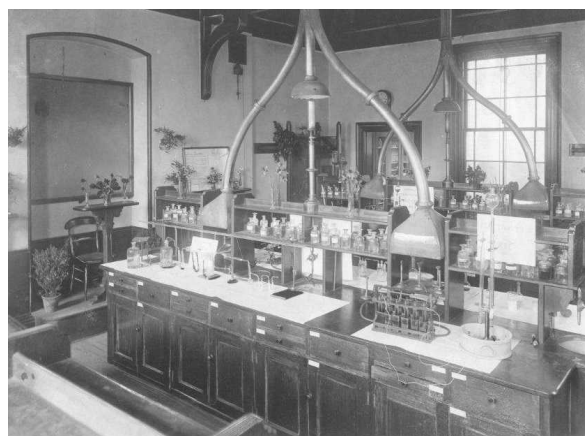


Figure 1. Chemistry laboratory at the North London Collegiate School, built in 1885, photo taken ca. 1890. Photo from North London Collegiate School Archives, by permission.

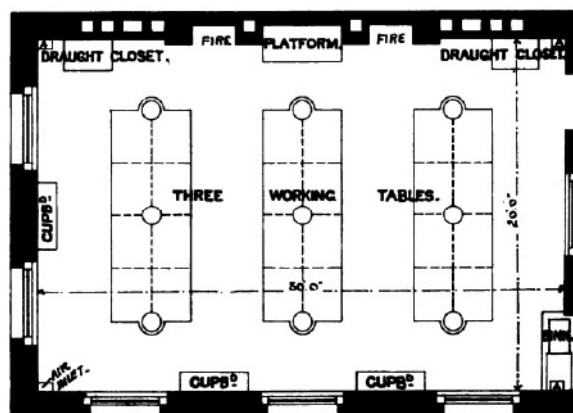


Figure 2. Plan of the chemistry laboratory at the North London Collegiate School, built in 1885. Plate 52, Ref. 18.

Schools of the Girls' Public Day School Company

The NLCS was regarded as a role model for subsequent independent girls' schools, to provide for girls an education comparable—or even superior—to that offered at the best boys' schools. In particular, the Girls' Public Day School Company (GPDSC) was inaugurated to provide a supervisory body for a network of girls' day schools (19). The first of these schools was opened in 1873 and others followed, many communities clamoring for their own GPDSC school. By 1900, there were 33 schools and a total of 7000 students. The central Council held sway in many matters, including curricula and many minutiae, including chemistry laboratories.

Though some of the GPDSC schools already incorporated a chemistry laboratory, in 1882, an edict went to all GPDSC schools that any new school building must incorporate a chemistry laboratory (20):

A chemical laboratory should be provided not less than 15 ft. wide and 16 ft. to 20 ft. long. It should be fitted with the necessary working tables and sinks. The ventilation arrangements should be similar to those in classrooms except that two shafts should be provided instead of one. One flue should be provided for ventilating the closet used for producing noxious gases.

The Council made it clear that costs were to be controlled (21):

They [the Council] recommend that in all Schools where there is practical teaching in Chemistry, a charge of not less than 5s. per Term shall be made for materials to each pupil doing Laboratory work,

and that all breakages shall be replaced by the pupil responsible.

Excellence in the teaching of chemistry was a major goal of the GPDSC as a means of establishing the academic reputation of their schools. To this end, a Conference on the Teaching of Science with Especial Reference to Chemistry (22) was organized by the Council in 1896, and chemistry teachers from all GPDSC schools were required to attend. There were two speakers, Ida Freund (23), the leading woman chemistry educator from Newnham College, Cambridge, and Henry Armstrong (24), of the Central Technical College (later part of Imperial College). Both speakers were fervent believers in the centrality of the laboratory experience for the teaching of chemistry. Armstrong proselytized his heuristic method of learning science. This form of learning through experimental work was, he contended, the only satisfactory way of truly understanding an experimental science, such as chemistry.

Following from the Conference, a detailed syllabus for the teaching of chemistry, including laboratory work, was produced by W. W. Fisher, Aldrichian Demonstrator of Chemistry in the University of Oxford (25). The complete listing of topics to be covered was circulated to all GPDSC schools. This was followed by a second conference in 1900 at which Armstrong again presented the arguments for the heuristic method of teaching chemistry (26). A further detailed syllabus for theory and laboratory work was published in 1902 and reprinted in 1912 (27).

Many schools took photographs of their new chemistry laboratories and, in some cases, photos showing students (and teachers). These photos give a fascinating insight into the facilities and into the experiments performed, even though some were clearly staged. Figure 3 shows the early chemistry laboratory at the GPDSC Shrewsbury High School for Girls. Titrations can be seen, while the teacher appears to be demonstrating gas collection. Despite the apparent enthusiasm, in 1900, the visiting GPDSC chemistry examiner at Shrewsbury, Dr. J. R. Green, was less than impressed with the one year's chemistry by the twelve girls in the 5th form class (28):

The girls, as a rule, remember the visible changes that occur in a particular reaction, but have no idea of the quantitative changes, and know practically nothing of what is actually taking place. For instance, they know that hydrogen is produced by the action of zinc on sulphuric acid, and know how to collect it, but know little about the quantity of gas produced from a given amount of zinc, and absolutely nothing as to the changes undergone by the acid or the zinc.



Figure 3. Chemistry laboratory, Shrewsbury High School for Girls, built in 1898, photo taken 1906. Photo from Shrewsbury High School Archives, by permission.

As each GPDSC school introduced laboratory work in chemistry, formal practical examinations were administered. The reports on these examinations were submitted to the Council of the GPDSC. For example, the 1886 report on chemistry examinations for Gateshead High School for Girls stated (29):

Division I. This Form took a paper on the South Kensington Advanced Course [in Chemistry]. Of the nine girls two were good, two moderately good, and the rest very weak. The same Form took a paper in Practical Chemistry. The work was, as a whole, extremely good, only two or three girls failing to find all the bases and acids set. The chief deficiency was in drawing conclusions from experiments, the results of which seemed in many cases not to warrant the conclusion arrived at.

Many GPDSC schools had already converted a classroom or other available space to a chemistry laboratory. The first chemistry laboratory at Oxford High School for Girls was a converted classroom, though it was used for a wide range of experimentation, from gravimetric and titrimetric quantitative analysis through to charcoal block and blowpipe qualitative analysis. A muffle furnace with exhaust vent is also visible (Figure 4).

By the 1900s, most GPDSC schools had a properly-equipped chemistry laboratory, but there were a few exceptions, one being the GPDSC Notting Hill and Ealing Girls' School. As shown in Figure 5, even in the 1920s, a classroom at that school was being used for practical chemistry. Along the window side-wall, it would appear that some reaction involving a drying U-tube is being employed.



Figure 4. Chemistry laboratory, Oxford High School for Girls, photo taken ca. 1900. Photo from Oxford High School Archives, by permission.



Figure 5. Chemistry class and laboratory session at Notting Hill and Ealing High School for Girls, photo taken in the 1920s. Photo from Notting Hill and Ealing High School Archives, by permission.

Practical Chemistry at Other Independent Girls' Schools

The Council of the GPDSC had clearly made practical chemistry a key part of the program at all of their schools. So did those of many other independent schools. Bedford High School for Girls was very highly-rated in 1900, having been chosen by the prestigious girls' magazine, *Girls' Realm*, to include in a series on outstanding British girls' schools. The author of the article, Christina Gowans Whyte, noted: "Two science laboratories are fully appointed for all grades. Practical work in chemistry is included in the curriculum" (30). Figure 6 shows the chemistry laboratory, constructed in 1887, with a distillation set-up in the foreground.

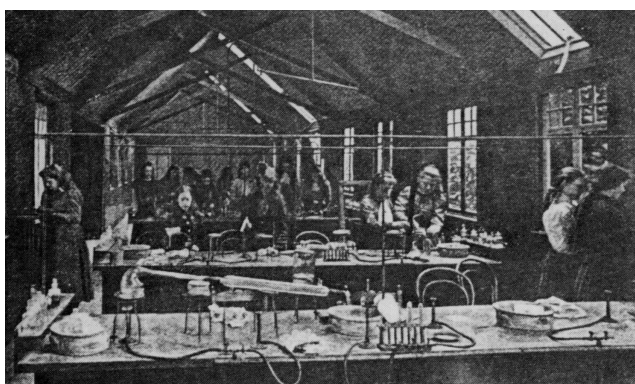


Figure 6. Chemistry laboratory, Bedford High School for Girls, built in 1887, photo taken 1902. Photo from Bedford High School Archives, by permission.

There were several books on chemistry experiments for high school students published during the 1880-1920 period. Perhaps the most authoritative version of required experimentation appeared as a series of lengthy articles in the journal, *School World*, in 1900 (31), following the syllabus necessary for the junior local examinations of Oxford and Cambridge Universities. The series starts with the distinguishing of a physical and a chemical change by heating a platinum wire, then a strip of magnesium, followed by observations of chemical changes by reacting iron and sulfur and also by heating mercury(II) oxide to give globules of mercury metal. All experiments were to be performed by the students themselves. Many of the later experiments revolve around gas collection, and Figure 7, the chemistry laboratory at Bedford's other girls' private school, the Bedford Girls' Modern School (later the Dame Alice Harpur School), shows the girls collecting and studying gases.



Figure 7. Chemistry laboratory, Bedford Girls' Modern School, photo ca. 1910. Photo from Dame Alice Harpur School Archives, by permission.

Even the smallest independent girls' school had to have a chemistry laboratory. Howell's School, Llandaff, Wales, was one example. The school authorities con-

structed a chemistry laboratory in an attic over a stable in the grounds of the school. Figure 8 shows a lonely student at Howell's School undertaking the ubiquitous acid-base titration.



Figure 8. Chemistry laboratory, Howell's School, Llandaff, Wales, photo ca. 1890. Photo from Howell's School, Llandaff, Archives, by permission.

By the 1920s, organic chemistry experiments were becoming more common and sophisticated. For example, Figure 9 shows a steam distillation in progress in 1925 at St. Leonard's School, St. Andrew's, Scotland.



Figure 9. Chemistry laboratory, St. Leonard's School, St. Andrews, Scotland, 1925. Photo from St. Leonard's School Archives, by permission.

The Decline of Practical Chemistry in Girls' Schools

Enthusiasm for practical chemistry seems to have waned by the 1930s. One cause was the concern of the significant costs versus limited benefit for most girls. Together with the tightening of finances, there was a greater emphasis on an education for girls toward the

roles of wife and mother and this demanded more time and resources for the domestic sciences (32). An additional reason was the lack of new chemistry teachers. Our research has shown that most of the chemistry teachers were born and educated in a narrow time-frame around the end of the 19th century. These pioneering women were enthusiastic about chemistry and devoted their entire adult lives to teaching chemistry. As they died, or in a few cases, married later in life, there seem to have been few in the post-suffragist era willing to see teaching chemistry as their sole future. In fact, the decline of chemistry did not happen at the same time at every school. A much better correlation can be found from the death or retirement of the chemistry teacher who had been at that particular school for decades. With the loss of these dedicated teachers, the existence of advanced chemistry courses at these schools in the early years often became forgotten.

The change in attitude can best be followed through the *Council Minutes* of the GPDSC. In a report of the Government Inspectors of 1922, it was stated that for the GPDSC Clapham High School for Girls: "Biology should be dropped in favour of more Chemistry and Physics, if the girls were to enter the Advanced Course as properly equipped as the boys." (33) Thus the focus at that period was on university-bound girls and equality with boys' schools.

By contrast, eight years later in 1930, a discussion took place among GPDSC science teachers on the teaching of biology in the GPDSC schools (34):

Miss Esdaile urged that Biology should be a compulsory subject, especially as such a small percentage of girls went on to Universities. ... Miss Haig Brown agreed that Biology was the best [science] subject for girls not going to a University. ... Miss M. E. Lewis and Miss Cossey said that Biology developed thought along interesting lines, made girls healthy and natural, and fitted them for public health work and social life.

And so this came to pass. For example, in 1931, it is noted that one of the GPDSC schools, Bromley High School, had dropped chemistry in favor of "General Elementary Science (Physics and Chemistry)," while another, Tunbridge Wells High School, was dropping chemistry for botany (35). By 1932, the general opinion of the GPDSC Education Committee was to replace the individual science courses by "General Science" (36). The change in emphasis become particularly apparent in the 1938 report for South Hampstead High School: "The only change in the curriculum this year has been the introduction of Cookery into the Lower Fifth and Sixth

Form Syllabus. This was made possible by the conversion of the old Chemistry Laboratory into a cookery-room and dining-room" (37). And, as the GPDSC schools were often the leaders, so it is likely that other girls' schools followed.

Commentary

We have shown in more detail that the teaching of chemistry, including a significant laboratory experience, flourished at British independent girls' schools between the 1880s and the 1930s. In addition to written accounts, we have collected visual evidence of the laboratories, a few examples of which have been shown here. In some photographs it is possible to deduce the type of experimentation. Reasons for the decline in chemistry teaching and, indeed, the "collective amnesia" of this era have been suggested.

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About the Authors

Marelene and Geoff Rayner-Canham have been active researchers into long-forgotten or overlooked early women chemists. Among the books they have authored are *Chemistry Was Their Life: Pioneering British Women Chemists, 1880-1949* (2008) and *Women in Chemistry: Their Changing Roles from Alchemical Times to the Mid-Twentieth Century* (1998). They were the editors for *Creating Complicated Lives: Women and Science at English-Canadian Universities, 1880-1980* (2012). Currently, they are undertaking a comprehensive study of the teaching of chemistry at pioneering British girls' schools.

WILLIAM GILBERT MIXTER (1846-1936): A YALE CHEMIST WHO DESERVES TO BE REMEMBERED

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Introduction

My great-aunt, Hilda Groening, was a pharmacist who graduated from the Melbourne College of Pharmacy in 1918 (1). The family pharmacy, where she worked with her father and mother, both qualified pharmacists, was not far from my home and it was there that I had my first exposure to chemicals and set out on the road to a career in chemistry. They were known, as pharmacists still are in Australia, as “chemists,” and the shop was a “chemist shop.” It was a traditional pharmacy, with globes of colored water in the window, and an extensive stock of *materia medica*. Patients were encouraged to bring their own bottles for what was often dispensed as “The Mixture.” Growing up in the 1940s, I was able to explore the organics, like liquorice root, and the inorganics like sulphur (always with a “ph”), copper sulphate, and Condy’s crystals and to play with the machine that squeezed corks down so they would fit into the customers’ bottles.

Although in the early twentieth century Australia was more closely linked to Britain than to America, the chemistry textbook that Hilda used in her training was an American one, *An Elementary Textbook of Chemistry* by W. G. Mixter (2). It is not clear whether this text was prescribed by the College or simply purchased by Hilda, but since Mixter’s book is not held in any Australian academic or public library it is likely that it was not one that a generation of students purchased. Texts

from an eclectic range of authors—but not including Mixter—were set for students at the nearby University of Melbourne’s chemistry school (3, 4) but there was a flourishing market for technical books in the city.

Mixter’s was my first chemistry book and I still have it. My evident interest in the subject was the reason that my parents brought me a chemistry set for my twelfth birthday. I soon accumulated other chemistry texts from second-hand shops. Later in life, when I became interested in the history of chemistry, I began to wonder about my first book: who was Mixter? and what he had contributed to the development of chemistry, apart from his textbook? Mixter was too late on the scene to be listed by Silliman (5) as a leading American chemist post-1845, his oeuvre amounting to only five articles by then. He was subsequently active in teaching and productive in research publication in a long career that I believe merits re-examination.

Biography

Obituaries for Mixter provide the outline of his life (6). He was born in 1846 in Dixon, Illinois, to George Mixter (Yale B.A. 1836) and his wife, Susan Elizabeth nee Gilbert. He graduated from Rock Island High School, Illinois, and went on to university study at Yale where he graduated Ph.B. in 1867. Although Yale had introduced the Ph.D. degree in 1860, many candidates took the three-year Bachelor of Philosophy degree, entry

to which did not require the Latin that was required for the B.A. (7). His baccalaureate degree was sufficient to gain Mixer an appointment as Assistant in Chemistry which he held for 1868-1870. He served as Instructor in Chemistry 1870-1872 and 1874-1875, the appointment being interrupted by two years spent in Europe, the first as assistant to R. W. Bunsen at the University of Heidelberg, and the second with A. W. von Hofmann at Berlin (8). It was common in the nineteenth century for American and British chemists to study in Germany, where chemical science was most advanced, without necessarily taking out a degree. Advancement in the profession did not always require an advanced degree, preferring study abroad to, for example, nascent Ph.D. programs at Johns Hopkins and Yale.

In 1875, at age 29, Mixer was appointed to a newly created chair of chemistry, and served as Professor until 1913, following which he was Professor Emeritus for 23 years until his death from bronchopneumonia. In 1875 he married Ada Louise Weber, who bore him a son and a daughter, but predeceased him by many years. In 1887 Mixer was awarded an M.A. (Hon) by Yale.

Mixer (Figure 1) was in charge of freshman chemistry at Yale for 38 years. He was (8)

more than a disciplinarian, more than a teacher of elementary chemistry. He was broadly and thoroughly trained in the science of chemistry, deeply interested in experimental work, and zealous in carrying on such research work as the time at his disposal would permit.

Upon Mixer's retirement in 1913, Yale's president, A. T. Hadley, wrote in his annual report that (9)

He was one of those men whom we could least afford to lose—eminent as an investigator, unremitting in his devotion as a teacher, and ideal in his relation as a man to his colleagues and to his students. I do not know which we shall most miss; his advice, his teaching, or his example.

Mixer's Published Research

Mixer published 33 single-author papers in the *American Journal of Science* which was founded by Benjamin Silliman Sr. in 1818, 19 in the *American Chemical Journal* founded in 1879 by Ira Remsen, two in the *Journal of the American Chemical Society* and two, arising from his work in Germany in the early 1870s, in European chemical journals. He divided his attention between organic chemistry, largely published in Remsen's journal, and thermochemistry, in the *American Journal of Science*.

His first publication concerned two silicate minerals found in a New Jersey mine (10). Willemite was a zinc silicate, $\text{SiO}_2 \cdot 2\text{ZnO}$, which owed its yellow or green color to a manganese impurity. Tephroite was the analogous manganese silicate, $\text{SiO}_2 \cdot 2\text{MnO}$, containing some zinc. Mineral chemistry and mineralogy were prominent in the work of the Sheffield School at Yale, influenced by Benjamin Silliman (1779-1865), his son, Benjamin Jr. (1816-1885), his son-in-law and successor James Dwight Dana (1813-1895) and Dana's son, Edward Salisbury (1849-1935).

Mixer's second publication (11) demonstrated a method for the estimation of sulfur in various materials by burning them in oxygen, passing the

combustion mixture over platinum gauze, exposure to bromine in hydrochloric acid to promote oxidation to SO_3 , absorption in water, and finally precipitation of barium sulfate. Coal, iron pyrites, crude sulfur, carbon disulfide, and wool were the materials studied. Oxygen for use in the assay was generated from potassium chlorate or potassium chlorate reacted with manganese dioxide, the latter being found to be contaminated with sulfur and thus requiring a blank determination. Sulfur-vulcanized rubber was avoided at critical parts of the apparatus. Concluding his paper, Mixer thanks Professors Samuel William Johnson, who taught agricultural chemistry at Yale 1857-1875, and the professor of analytical chemistry, Oscar Dana Allen, for assistance and suggestions.



Figure 1. Portrait of William Gilbert Mixer by Huc-Mazelet Luquiens (1914). Yale University Art Gallery. Gift of George Mixer, Ph.D. 1895 and Mrs. Henry Galpin to the Sheffield Scientific School.

The abstractor for the *Chemical News* (12) noted that it was not possible to understand Mixer's work without seeing the woodcut in which the apparatus was depicted, whereupon the journal reproduced the whole of the paper in a subsequent issue (13). Almost a decade later, Mixer returned to the analysis of sulfur, this time in gas streams, and suggested refinements in the methods employed by him and other chemists (14, 15).

Although abstracted in the *American Journal of Science* (16), Mixer's next paper, on specific heats of three elements, was actually published with his collaborator, E. S. Dana, in Justus Liebig's *Annalen* (17). The authors note that the determinations were carried out in Heidelberg, in the laboratory of Robert Bunsen, whom they thank for support and encouragement. Thermochemistry was to become a major activity for Mixer, but his exposure to organic chemistry in Berlin (18) kindled an interest in a second field of research in which he was to publish extensively. Three papers in the *American Journal of Science* and one in the *American Chemical Journal* in 1877-1879 described the preparation of silver ammine sulfates and nitrates from aliphatic and aromatic amines, and an accompanying paper from Dana described the crystal habit of hydrated and anhydrous forms of one of Mixer's compounds (19). Before the days of X-ray diffraction, of course, "crystallography" consisted of the classification of gross crystal habit and measurement of the interfacial angles.

Between 1879 and 1893 Mixer did not publish in the *American Journal of Science*, but instead sent his manuscripts to Remsen's *American Chemical Journal* and it was there that the bulk of his organic chemistry (16 papers) was published. Six of these papers, all dealing with the chemistry of acyl-anilides (1886 to 1889), were published with his graduate student co-authors, Thomas Burr Osborne, Conrad Henry Matthiessen, Joseph Osterman Dyer, Frank Otto Walther, Charles Percy Willcox, and Felix Kleeberg. Most took the Ph.B. degree and subsequently took medical or law degrees at other universities. The outstanding career was that of Osborne (1859-1929) who took the Ph.D. degree in 1885 and was assistant in analytical chemistry in the Sheffield School 1883-1886. For forty two years he was employed as a biochemist at the Connecticut Agricultural Experiment Station where his investigations concentrated on vegetable proteins, but he was also the co-discoverer of vitamin A (20).

Resuming publication in the *American Journal of Science*, Mixer published two papers on what he called "electrosynthesis." He reported on the products

of reactions between gases that were exposed to electrical discharge in the kind of apparatus used to generate ozone from oxygen, which he described first as a "feeble alternate discharge" and later as a "glow discharge" between the glass walls of a eudiometer surrounded by a water jacket. The reactions took place at temperatures far below those where the gaseous molecules would dissociate. In the first experiments (21), water and dry carbon monoxide ("carbonic oxide") reacted slowly to form carbon dioxide. Methane, ethane, ethylene and acetylene, exposed to oxygen were wholly or partly converted to carbon dioxide and water. In a second paper (22) Mixer reported that oxygen and hydrogen combined to form water, while a mixture of oxygen and ammonia formed ammonium nitrite that was deposited as white coating on the walls of the apparatus.

After the turn of the century, Mixer embarked on a series of researches with gases and gaseous mixtures, in the first of which (23) he explored the thermal decomposition of acetylene and other "endothermic gases"—cyanogen and nitrous and nitric oxides. Turning to explosions of mixtures containing oxygen (24), he found that below certain pressures the reactions were not self-propagating, the reason for which, he hypothesized was the "infrequency of impacts of molecules having velocity or internal energy adequate for chemical union." Such a view places Mixer in the mainstream of physical chemistry where the kinetic theory of gases was developed (25), and although his approach was non-mathematical, it may have benefitted from the presence, "working in splendid isolation at Yale University" (26) of J. Willard Gibbs (27). Further investigating the explosion of acetylene-oxygen mixtures, Mixer noted the presence of acetylene in the mixture after the reaction and ascribed this not to residual, unconsumed acetylene but to subsequent re-synthesis, in support of which he reported also the presence of a compound of carbon and nitrogen that had been formed in the eudiometer (28). He then showed that hydrocyanic acid was formed during explosive reaction of acetylene and ammonia (29).

Mixer then commenced a series of researches on heats of reaction and heats of formation of metal oxides. The oxidant was sodium oxide (sodium peroxide), which enabled him to conduct oxidations that were not accessible with molecular oxygen and to calculate results based on the known heat of formation of sodium peroxide for cases where other methods such as heat of neutralization were not applicable (30). In the following paper (31) of what turned out to be a series of 18 papers over the next 17 years, he announced his aim "to determine if the

position in the Periodic System and the magnitude of the atomic weight of the element have a marked influence on” the heats of such reactions. This proposal was examined in a detailed review (32) of his own and other researchers’ results—notably those collated by Julius Thomsen (1826-1909) (33). He observed that within sub-groups there was good linearity between atomic weight and heat of oxidation, and that anomalies might be due to errors in experimental results that called for further investigation. He also urged attention to the thermochemistry of rare elements.

His final thermochemical paper (34) was an overview of reactions involving sodium peroxide, “the only way known for finding the heat of oxidation of elements which do not burn in oxygen and which form oxides insoluble in acids.” In it, he described his experimental methods in great detail, and noted that “the sterling silver bomb weighed when made 472 grams and after eight years’ use 465 grams. The loss is due to corrosion, especially by sulfur, and to polishing.”

While the bulk of Mixter’s publication after 1895 was in the *American Journal of Science*, he published two papers in the *Journal of the American Chemical Society* and the chemistry described in them was quite different from those of his major series on organic chemistry, gaseous reactions, and inorganic thermochemistry. The first of these “outliers” (35) concerned a translucent ruby-red deposit formed on a gold electrode during electrolysis experiments, which Mixter showed to have arisen from oxidation of the metal. In the presence of appropriate solutes, auric hydroxide, potassium hydrogen aurate, basic auric sulfate, and a fulminate could also be formed. The second paper (36) described a qualitative test for carbon developed by his late colleague, Professor S. L. Penfield (37). The test consisted of fusion of the test sample with lead chromate in a narrow hard-glass tube, and placement of a drop of barium hydroxide solution further along the tube where it could intercept any carbon dioxide emitted by the fusion mixture. Meticulous as ever, Mixter noted that the test was “so delicate that lead chromate that has been exposed to the air in preparation will react for carbon from dust in the air.” To judge from its absence from Feigl’s compilation (38), the Penfield test was not widely adopted.

Mixter’s Textbook

Mixter’s textbook (See Ref. 2) was first published in 1888, with successive editions incorporating revisions in 1889, 1890, 1893, and the fifth and final edition in 1897.

Following digitization by the Library of Congress it is available on-line (39), and has recently been republished in paperback. The unsigned review published in the *American Journal of Science* was complimentary, briefly summarizing the contents and noting that it “presents the general facts and principles of the science under a succinct form and a sensible arrangement well adapted for its purpose” and that “the volume is handsomely printed and the illustrations are excellent” (40). Another friendly review appeared in *Scientific American* (41), saying that the book gave “a very complete view of the bases of the science of inorganic chemistry” and praising the illustrations. A less complimentary account appeared in *Chemical News* (42), where the reviewer pointed to “one feature of distinction from the almost endless array of chemical manuals—it is based on the periodic classification” but qualified this praise with “Strangely enough we can find in it no mention of the originator of this system, Mr. Newlands!”

Mixter’s professorial colleague Charles S. Hastings (43) contributed the sections on the Physics of Chemistry (pages 1-45) and Spectral Analysis (pages 90-94). His major section covered fundamental concepts including units, forms of matter and use of the balance, temperature and heat, and devoted 12 pages to each of crystallography and gases (pressure, volume, laws, kinetic theory, diffusion, gas density). The spectroscopy section drew on the work of Bunsen and Kirchhoff, Hastings having attended the lectures of Kirchhoff in Heidelberg in 1874.

Mixter began his chemistry section with a list of the 68 elements recognized up to the year 1888, together with their atomic weights. Mixter acknowledged the existence of other forms of the periodic classification, but chose to reproduce Mendelejeff’s [*sic*] so-called “vertical table” of the kind first published in 1869, with the periods appearing in columns, while the groups run horizontally across the page, rather than the now more familiar “horizontal” version of 1871 (44).

The main text begins with hydrogen, and then come the elements and their compounds in their Groups, in the order VII, I, VI, II, V, III, IV and VIII. The reason for this idiosyncratic order allows Mixter to cover, in a particular group, only those compounds which an element forms with elements in previous groups. This cumulative approach is enriched by occasional inter-Group essays, devoted to valence; bases, acids and salts; atomic theory; and the periodic law. In the penultimate essay Mixter takes a stance on the question “do atoms exist,” noting that “the atomic theory is in accord with all facts and laws of physical and chemical science” and must be “regarded

as established ... until facts are discovered which are clearly at variance" with it.

Perhaps acknowledging that his arrangement of material is unusual, Mixter advises students to use the index (11 pages) and adds that they may wish "to look up the properties of many substances before studying them systematically." He also recommends to such students that they might wish to "refer to larger works such as Roscoe and Schorlemmer's *Treatise on Chemistry*, and Watts' *Dictionary of Chemistry*, for in doing so "will early form the invaluable habit of using the literature of chemistry."

For purposes of comparison I have chosen the presentation of material in a contemporary text, *Watts' Manual of Chemistry* (45). When Tilden took over publication of this classic, his first edition included over 100 pages of the physics "which properly precedes the study of chemistry," but in his second edition, faced with the need for even greater coverage of physics at the expense of pages that could be devoted to chemistry, he greatly abbreviated this. Like Mixter, Tilden intersperses the sections on groups of elements with chapters on chemical affinity and combination, crystalline form, spectral analysis, and atomic theory including the periodic classification. The organization of the main body of material is quite different, however. He begins with non-metallic elements, covering hydrogen and the halogens (including their hydrides and oxyacids), oxygen and the sulfur/selenium/tellurium group, carbon and silicon, and nitrogen/phosphorus/arsenic. Although there are fewer illustrations, Tilden's coverage of the chemistry is more extensive than that in Mixter's elementary text and it is clearly written for more advanced students. He dealt with the chemistry of metals in groups such as alkalis and alkaline earths, and those headed (typified) by magnesium, lead, copper, iron, chromium, tin, antimony and platinum. In most of these, the group includes what we now regard as main group elements and those members of sub-groups with similar combining power.

Concluding Remarks

As the reviewer for the *Chemical News* observed, rather tetchily, the nineteenth century saw "an almost endless array of chemical manuals" many of which are still to be found in second-hand bookshops, for sale through the internet, and in some cases accessible electronically in digital format. Mixter's textbook is not remarked on these days although it must have enjoyed considerable esteem because it ran to five editions. Nor is his research cited,

probably due to advances in thermochemical methods that have produced better data.

Dying in his ninetieth year, Mixter had long outlived most of his contemporaries although he was remembered at Yale (46) and there were brief but generous obituaries (47, 48), in which it was stated that "his data in branches of thermal chemistry have become international standards." He is mentioned in biographical compilations (49, 50) and in lists of American chemists who worked with Robert Bunsen. In one of these (51), he is listed among a "few of the better known chemists of the U.S.A.," but this was insufficient recognition to gain this innovative and productive chemist a lasting place in the pantheon, and he does not appear in either of Miles and Gould's volumes on American Chemists and Chemical Engineers (52).

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OUROBOROS, A NEW ENGLAND CHEMISTS' CLUB (1)

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At a meeting of the Northeastern Section of the American Chemical Society in Boston, December, 1909, a group of chemistry professors proposed the formation of a "Chemistry Round Table." Its purpose was to provide the opportunity for New England college chemistry teachers to convene and to exchange information and ideas about their profession. This notion had its roots in an earlier but vaguely defined "Chemical Club," whose original members were Edwin J. Bartlett, Dartmouth; Leverett Mears, Williams; Leonard P. Kinnicutt, Worcester Polytechnic (WPI); John T. Stoddard, Smith; and Henry P. Talbott, MIT. It was Kinnicutt of WPI who was the chief proponent of this move.

For an organization that has been typified through the years as unstructured and sometimes leaderless, this founding group moved quickly. Within a year of the original proposal, the first official meeting of the club was held at the Draper Hotel, Northampton, MA, with Professor Stoddard of Smith College as host. Ironically, Professor Kinnicutt, the prime mover, was not present but sent W. L. Jennings of WPI in his place. The seven official original members (including the absent Kinnicutt) represented Amherst, Massachusetts College of Agriculture, WPI, Williams, Smith, and MIT. A year later, at the second meeting held at the St. Botolph Club, Boston, six additional members from Dartmouth, Holy Cross, MIT, and Amherst, joined the club. Upon the death of Kinnicutt in 1911, membership consisted of 11 individuals from nine institutions. Information on the early meetings of

the club is indeed sparse, for, only at the ninth meeting in 1914 was a vote taken to keep records of minutes and attendance. Indeed that has been carried out scrupulously ever since. The minutes of all meetings through No. 160 have been preserved in the possession of the club's only officer, known for at least the past 50 years as "Custodian of the Archives." Abstracts of the minutes were published in a series of six volumes (2). Most of the material being presented comes from these invaluable documents.

To describe the structure of the organization is not only difficult but perhaps inappropriate. While it was clear from the start that the objective was to bring together teachers of chemistry in New England, the group has never adopted a constitution or set of bylaws in its 92-year existence. A "tentative constitution" was drawn up, probably in 1923. (A copy is to be found in the private papers of Charles James, University of New Hampshire, elected in 1922.) No further mention of the document appears in any subsequent minutes. A fragment of what may be a revision includes the name of George Scatchard, MIT, who was elected in 1926. Among the features covered in this proposed constitution:

Membership: any **male teacher of chemistry** in an institution of **college or university** rank, or person interested in teaching chemistry, **residing in New England.** (not to exceed 30).

Meetings two each year, fall and spring. "No formal papers or lectures shall be presented at a regular meeting, except with the unanimous consent of the members present."

Object: to provide an opportunity for social fellowship and informal fraternizing upon things chemical.

Arthur Lamb of Harvard had his own clever version of the objects of the club, recorded in the official minutes: “coadunation [union], libation, deglutition [swallowing], disputation, and cachinnation [immoderate laughter].”

An official name for the organization was not even considered (according to existing minutes) until 1915. Among the suggestions were “Chemical Academy,” “Chemical Round Table,” and “Ouroboros Club.” At the May 1916 meeting, the last was “favored,” according to the minutes. Whether any formal vote was in fact taken is not recorded. So, after six years, the organization had a name: Ouroboros Club; over the years this has been shortened to “Ouroboros.” What does it signify? According to the Larousse encyclopedia (for it is not to be found in unabridged dictionaries or, indeed, in most encyclopedias), the Greek ouroboros is a circular serpent poised with the tail in its mouth and signifies the totality of nature and the union of heaven and earth. At the Boston meeting of Ouroboros in 1918, Professor Hopkins, Amherst, made a presentation on the significance of “our serpent Ouroboros.” In Greek letters it is rendered: Ουροβόρος. The tail-eating serpent, supposedly of Phoenician origin, has been variously viewed as a symbol of science, the alchemist’s distillation vessel, and even of magic. According to Egyptian and Greek legend (*Britannica*), the serpent is continually devouring itself and being reborn from itself. Inside the circle is the legend: εν το παν, transliterated “HEN TO PAN” — “One is the All.” The alchemist Zosimos provided a more extended version in a technical recipe:

One is the all
By it the all;
For it the all, and
In it the all.



Figure 1. Ouroboros depicted in an illustration from the work of Cleopatra the Alchemist.

In subsequent meetings members occasionally brought up the subject of their club’s name: its origin, its meaning, and even debate over its transliterated spelling; but no conclusions were ever recorded. Member Donald Hornig (Brown University) named his boat “Ouroboros.” The hosts at Clark University in 1966 carried the Ouroboros theme to its extreme by publishing the dinner menu with Greek letters.

Without constitution or bylaws, and thus united neither by a set of officers nor a treasury, Ouroboros was self-perpetuating through the one and only recognized continuing official. Described in the minutes of a 1924 meeting as “custodian” and later occasionally as “permanent secretary,” the officer eventually became the “custodian of the archives.” Biannual meetings have typically been arranged by an Ouroboros member at the designated host institution. This host (in early years dubbed “temporary secretary”) sent out invitations to members and guests (named by the nominating committee for possible election.), together with a program for lunch, afternoon activities, dinner, and an evening discussion session. A typical example was the gathering at Dartmouth in 1921 at the Outing Club (Figure 2). Arrangements were also made for entertainment of nonchemist guests (i.e., spouses). Following the meeting, a ballot for new members was sent to those Ouroboros members who had attended. The host also sent a bill of reckoning for the costs of food and libation, recorded minutes of the meeting, and then passed on the records to the following host.

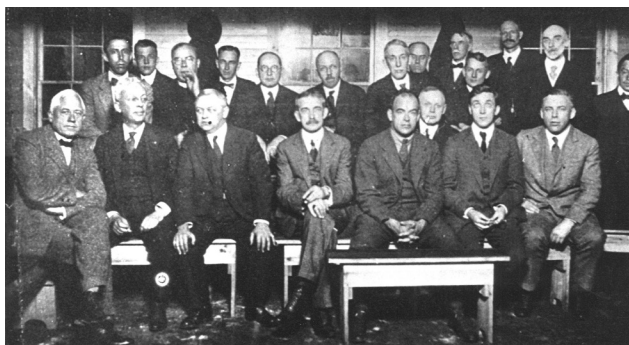


Figure 2. Attendees at the Ouroboros Meeting in the Dartmouth Hut, October 1921.

Election of members was a topic discussed at many meetings over the years, with regard to number and method of election. The early limit in membership varied from 20 to 35; but after World War II the active members increased substantially. Three or more negative votes were required to exclude a nomination, according

to action taken at a 1928 meeting. Until the late 1960s the **qualification** for membership never changed: members were to be men teaching chemistry in New England! Membership has at times included one or two chemical engineers. If a member moved from the New England area or retired, he became "honorary." In 1969 a motion was proposed to elect women; it passed by a vote of 24 to 3! The next year the first woman, Anna Jane Harrison (Mt. Holyoke), was elected to membership in Ouroboros. She served as the first female president of the American Chemical Society in 1978. The first election to Ouroboros of a husband and wife (Nancy and Thomas Lowry) took place in 1975.

Over the course of 85 years, Ouroboros meetings were scheduled regularly each spring and fall, with no exceptions from 1916 to 1968. None took place in 1983 or 1993. Amherst College served as host 17 times; Dartmouth 15; Yale 14; Worcester (alone or jointly with Clark) 14; Brown 13; Bowdoin 12. Smith hosted two meetings in the first decade but never thereafter. A dozen or so other schools served as hosts as well. Vermont, represented by a member for the first time in 1972, hosted its first meeting in 1977. At the last meeting at Bowdoin in 1994, 16 came for lunch, 18 for dinner (this included spouses).

The roster of Ouroboros members includes three Nobelists (T. W. Richards, elected 1915 (Nobel laureate 1914); Lars Onsager, elected 1957 (1968); W. N. Lipscomb, elected 1965 (1976)). Not all Nobel chemists in New England institutions were members, however. Among Ouroboros members, two served as college presidents and 11 as presidents of the American Chemical Society (one, Arthur Lamb, serving twice) in the span from 1904 (A. A. Noyes) to 1978 (Anna Jane Harrison).

What took place at the 160 meetings over eight decades of the 20th century, besides libation and cachination? An enumeration of some of the recurring topics opens a window into the evolution of American chemistry and the mutual impact of the profession and society on each other. Let us listen in on the evening discussion sessions in each decade:

TOPICS DISCUSSED:

1920s

- Requirements for M.S.
- How to present chemistry to nonscience students
- Research ethics
- How to get rid of women students gently!

- J. B. Conant: account of visiting 25 German labs (1925)
- Reduction of chemistry courses in chemical engineering curriculum!
- Ph.D. exam

1930s

- Math preparation for chemists
- Norris proposed Richards Medal (1930, T. W. Richards died 1928)
- Teaching chemistry without lab
- Chemists as consultants—fees
- Chemistry curriculum:
 - General content
 - Physical chemistry in first year
 - Micro- vs. semi-micro analysis
 - Importance of history of chemistry in curriculum
 - Language exams
 - Teaching good English
 - ACS standards
 - Honors courses
 - Honors College
- Academic Calendar
- Selection of Ph.D. candidates—eliminating those incapable!
- Faculty salaries
- Effect of depression on chemical industry
- Increasing ACS dues
- High price of German journals
- College entrance exams
- Increasing enrollments
- Lecture demonstrations (live, by Kistiakowsky and Fieser)

1940s

- Retirement age for professors
- Defense courses
- Effect of war on college curriculum (Conant, others over several meetings)
- Liberal vs. practical education
- General science for B.A.s
- Postwar influx of students
- M.S. at liberal arts colleges
- Financing ACS
- NSF support of research
- Government contracts

1950s

- Freshman course for nonscientists
- Lack of appeal of chemical industry for students
- Importance of undergraduate research for inspiration
- Science vs. humanities (“Two Cultures??”)
- ACS accreditation for graduate schools
- Disappearance of quantitative analysis
- Continuing shortage of chemistry students
- NSF support for high school teaching (summer institutes)
- Teaching by graduate students—condemned
- Visual aids for teaching
- Ramifications of conversion of teacher’s colleges to liberal arts colleges
- Chemistry libraries—should be kept separate from main libraries
- Advanced placement

1960s

- Outreach for teaching chemistry: UNESCO
- NSF URPP
- Time demand on faculty writing proposals
- Public image of chemistry
- Expansion of Ph.D. programs—feasibility at smaller schools
- Academic calendars
 - Dartmouth plan
 - January program
- Curriculum:
 - Physical versus inorganic approach in freshman chemistry
 - Advanced placement
 - Teaching relevance of chemistry
 - Incorporating pollution, environmental issues
- Student Riots

1970s

- Reduction in graduate enrollment but increase in chemistry enrollments
- Shift in NSF funding from fundamental to applied research
- Curriculum
 - Incorporate more biology, biochemistry
 - more descriptive chemistry!
 - More preparation for chemical industry
 - ACS certification
 - Need for more analytical chemistry

- Opening of student records to students and parents
- Chemical waste: dealing with OSHA and EPA (repeated topic into 1990s)
- Increased cost of laboratory instruction: closed circuit TV; instrument costs
- No substitute for laboratory!
- Faculty unionization
- Dispersal of overhead funds

1980s

- Council for Chemical Research (academic/industrial interface)
- Shortened academic calendar
- Equipment for small schools
- Incentive grading
- Growing use of personal computers
 - Role in undergraduate teaching
 - Role in laboratories
 - Role in lectures
- Concern for high school teaching, also K-12
- Academic teaching labs for 21st century

What role did Ouroboros play in New England chemistry? To be sure, many of its active members were leaders at their own institutions (often heads or chairmen), who were able to commiserate with their colleagues twice a year on subjects of common interest in chemistry. I would like to think that the discussions helped to formulate points of view and values and to provide encouragement for these teachers and researchers to return to their own institutions with reinforced conviction about their policies and methods for accomplishing their goals. The organization also served as an opportunity for socializing with chemistry colleagues, who all became better acquainted and probably were more inclined to communicate with each other between meetings. A particularly congenial gathering was photographed during a visit to the Worcester Foundation for Experimental Biology in 1947 (Figure 3).

No meeting has been held since 1994. At that time there were 34 active members on the roster, even though honorary members (either retired or removed from New England) numbered 44, and 90 members were deceased. Thus, from a charter group of seven far-sighted New England chemists in 1910, the full, cumulative roster of members elected to Ouroboros finally totaled 168 (3). Just as the organization came into existence with

no official document or formal declaration, so it expired without a notification to members nor any written decree.



Figure 3. Gathering of Ouroboros members at Worcester Polytech, May 1947.

Acknowledgment

I am grateful for considerable help from two honorary members of Ouroboros noted here. The late Edward R. Atkinson, author of several of the volumes of Ouroboros history and a walking archive himself, offered invaluable assistance in this presentation. I thank Fred Greene, "Custodian of the Archives," for providing photographs and other materials from the master files.

References and Notes

1. Presented in a symposium, "Impact of Chemistry on the History of New England," 224th National Meeting of the American Chemical Society, Boston, MA, Aug. 19, 2002.
2. Walter L. Jennings, Meetings 1 (1910) to 59 (1940); Ernest D. Wilson, Meetings 60 (1940) to 80 (1950); Edward R. Atkinson, Meetings 81 (1951) to 110 (1965), 111 (1966) to 135 (1978), 136 (1979) to 150 (1987), and 151 (1988) to 160 (1994). The late Dr. Atkinson provided copies of the minutes to the author.
3. Dr. Atkinson maintained a continuing current roster of membership (personal collection).

About the Author

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HISTORY OF CHEMISTRY IN THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

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Supplemental material

Abstract

The origins of the Laboratory of Bioorganic Chemistry, NIDDK, NIH can be traced to events that occurred in the early 20th century. From its beginning to the present, as the laboratory evolved through several organizational changes, many important historical contributions to organic chemistry and biochemistry were made. For example, its early precursor, the Division of Chemistry of the Hygienic Laboratory, was assigned the responsibility of safeguarding public health by analyzing environmental and other chemical risks. This review will trace important developments from the early 20th century to the present. The topics covered in this review include a historical synopsis, early work on receptors, carbohydrates, heterocycles and nucleotides, with specific emphasis on frog skin alkaloids, the NIH shift (a transfer of an aromatic hydrogen atom to a neighboring ring position during ring hydroxylation, important in the biochemical processing of aromatic substrates), the methionine-specific cleavage of proteins using cyanogen bromide (used commercially and in peptide research) as well as other fundamental contributions. Ongoing research in medicinal chemistry, natural products, biochemistry, vaccines and pharmacology, some leading to clinical applications, will be discussed.

Introduction

The National Institutes of Health (NIH), with headquarters in Bethesda, Maryland, USA, is the largest biomedical research institution in the world, with approximately 7000 researchers supporting basic and “bench-to-bedside” translational research (that is, practical application of basic science to enhance human health). The NIH, including its Intramural Research Program (IRP), is almost wholly supported by the US Federal Government, in recognition of the benefits of basic biomedical research to public health. Dozens of pharmaceuticals have been developed and introduced to the market with the direct participation of NIH scientists (1). Additionally, development of countless pharmaceuticals has been facilitated by novel concepts discovered at NIH and published in the research literature. Thus, the NIH IRP has provided many basic research discoveries that have been and continue to be instrumental in the discovery and development of new medical treatments and diagnostics. The NIH IRP has also played an important role in the mentoring of American and foreign scientists through its training programs.

Although only a handful of the laboratories inside NIH are focused primarily on medicinal chemistry, these research groups, including what is now the Laboratory of

Bioorganic Chemistry (LBC) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), have a major historical impact. This report describes the contributions of many chemists to the research of this Institute, including the unique roles of key researchers in the development of organic chemistry in NIDDK. Within this laboratory, there have been major efforts, both in the past and present, on G protein-coupled receptors (GPCRs) and ion channels, natural products, carbohydrates, anti-infective drugs, nucleosides and nucleotides, and heterocycles. Specifically, such topics as toxins that act at ion channels, receptors for drugs of abuse, biogenic amines, carbohydrates, and purine receptors are discussed here. We provide a synopsis of each of these diverse areas of research associated historically and currently within this laboratory.

Early Historical (Chronological) Perspective

This section discusses the origins of the organic chemistry laboratories of NIDDK. These laboratories include what are now designated as the Laboratory of Bioorganic Chemistry (LBC) and the Laboratory of Medicinal Chemistry (LMC), which have origins within a common progenitor, the Laboratory of Chemistry (LC) (Figure 1). In order to understand the origins of the LBC, it is necessary to trace the reorganizations within NIDDK (nee NIAMD, National Institute of Arthritis and Metabolic Diseases) that resulted in the current makeup of

these organic chemistry laboratories. These laboratories were direct descendants of the Division of Chemistry of the Hygienic Laboratory of the US Public Health and Marine-Hospital Service (shortened to Public Health Service in 1912) in Washington, DC (2-7).

The precursor to NIH was the Hygienic Laboratory, which in 1891 moved from New York City (where it was concerned with immigrant health) to Washington, DC, where it adopted a broader role in evaluating scientific factors affecting public health. The importance of chemistry in the context of US government biomedical research became apparent in the early decades of the 20th century, especially with increased understanding of the role of chemistry in living processes. This was accentuated in Nobel prizes during that period (6, 8). Thus, the early precursor of LBC, the Division of Chemistry of the Hygienic Laboratory, was founded in 1905 and assigned the responsibility of safeguarding public health, which came to include analyzing environmental and other chemical risks and developing chemical diagnostic tests. The laboratory evolved through several organizational changes and its eventual move to the current location in Bethesda, MD, where it made many historically important contributions to organic chemistry and biochemistry.

The Division of Chemistry was established through an Act of Congress in 1902, although it began work in 1905 (6, 7). The reorganization legislation added three

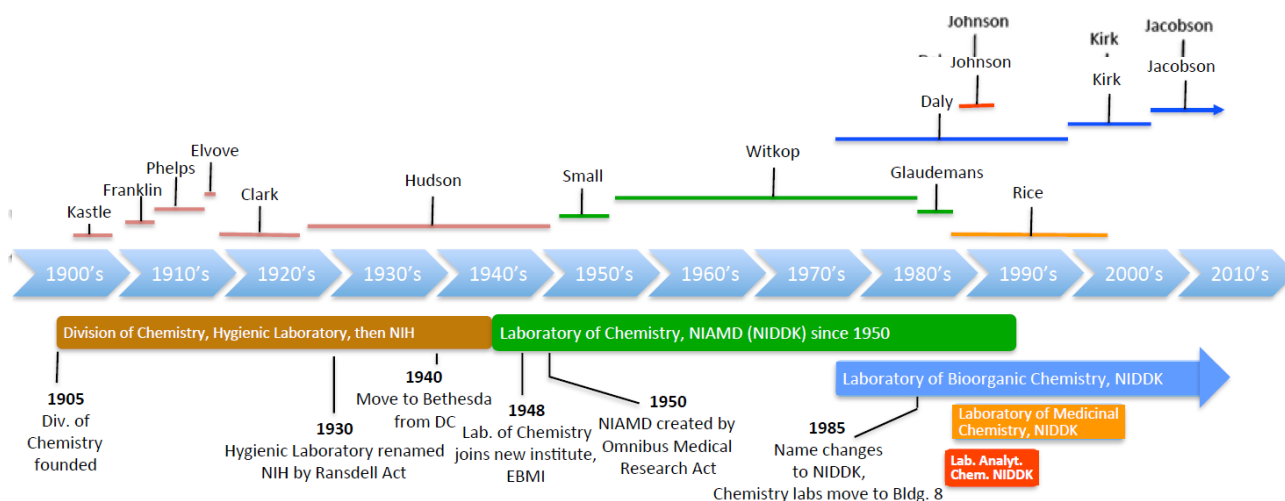


Figure 1. Timeline of leadership (upper) and organization (lower, shade matched to leadership) of the organic chemistry laboratories of NIDDK and its precursor institutes. At the time of its founding, the Division of Chemistry of the Hygienic Laboratory was located near the present location of the Kennedy Center at 25th and E Streets, in northwest DC (2). The name of the Institute that later housed the former Division of Chemistry was changed from NIAMD (since its creation in 1950) to NIAMDD (1972), to NIADDK (1981) and then to NIDDK (1986).

new Divisions to the Hygienic Laboratory. The existing staff, already authorized to work on infectious diseases, was designated the Division of Pathology and Bacteriology, and new Divisions of Chemistry, Pharmacology and Zoology were added to fill gaps in expertise needed for a comprehensive biomedical service organization. The Chiefs of the Divisions were to be prominent scientists who were given the title "Professor." Laboratory staff worked 48 hours per week including Saturday, and research reports were published in a dedicated periodical *Bulletin of the Hygienic Laboratory* and in *Public Health Reports*, in addition to general scientific journals (7, 9).

Questions that concerned chemists in the early days of the Division of Chemistry include: What makes fireflies glow? Do ingested medicines contaminate mother's milk? Why do people who drank alcoholic ginger extract during Prohibition suffer from limb weakening? How can we detect the presence of blood at a crime scene? Is fluoride in the drinking water good or bad for teeth? Thus, the Division of Chemistry initially had a responsibility to safeguard public health by studying environmental and other chemical risks, including analyses of adulterated food, water, milk, drugs and other substances. At first, the Division also provided essential chemical expertise, rare at the time, to other biomedical researchers (3) such as physician Joseph Goldberger of the Hygienic Laboratory in his classical studies of pellagra. The Division also collaborated with the Department of Agriculture, which was responsible for implementing the 1906 Pure Food and Drug Law.

The first Chief of the Division of Chemistry in 1905 was Joseph Hoeing Kastle (1864-1916), a prominent and enthusiastic educator from the University of Kentucky, (Figure 2), who held the position until 1909 (10). He encouraged the staff to cooperate with other Divisions to solve problems of public health, including routine



Figure 2. Early Chiefs of the Laboratory and their years of service (photos E. Elvove).

analyses needed by the US Public Health and Marine-Hospital Service (6). Kastle invented a test for the presence of blood on forensic samples based on an enzymatic oxidation leading to a pink color reaction of reduced phenolphthalein indicator in a basic solution (Kastle-Meyer reagent) (11).

His methods for measuring hydrochloric acid in the stomach

(Kastle's reagent) (12) and hemoglobin in blood became standards in the field and he devised methods for determining saccharin and components of spices (13). He coauthored a study of typhoid fever in Washington, DC, with bacteriologist M. J. Rosenau and epidemiologist L. L. Lumsden of the Division of Pathology and Bacteriology (14). During this period, one of the more exotic projects was the extraction of the glowing principle of fireflies, but the work fell short of the characterization of the enzyme luciferase (15).

Kastle departed the Hygienic Laboratory after four years, displeased with the small staff, low salaries and inadequate resources for the work needed, and returned to academia (6). After a two-year interim without a Division Chief, Kastle was succeeded by Edward Curtis Franklin (1862-1937), who served from 1911-1913 (16) before returning to Stanford University. While Franklin continued Kastle's investigation of "ammonia systems," the Division continued to do analytical work, and, according to an internal report written by Elias Elvove (3) (1883-1962, Figure 3 (upper)), prepared several grams of pure tryptophan as a standard. Franklin also studied the radioactivity of the thermal springs in Hot Springs, AR, to which were ascribed curative powers. Other work consisted of abstracting scientific papers, expert testimony in court, examining the food value of a powdered infant formula called "Mammala" at the request of the War Department,

and giving highly sought public lectures (approximately monthly) sponsored by universities, other government labs, and scientific societies. His support staff consisted of one scientific assistant (Elvove), a general helper, and a glassware/laboratory cleaner.

Earle Bernard Phelps (1876-1953), already an expert on water sanitation, was chosen to serve as Chief in 1913 and served until 1918 (3, 6). He was a graduate of MIT, but with no degree more advanced than a B.S. in chemistry. In response to rising concern about industrial pollution in the United States, he studied water pollution, chlorination and waste biochemistry. Under Phelps, analytical work in the Division continued with published articles such as "The Chemical Measures of Stream Pollution and Specifications for Sewage Effluents" and "Chemical Studies of the Pollution of the Ohio River," which described research that studied re-aeration and the oxygen demand of organic pollution (17, 18).

When Phelps left the position, Elvove briefly served as Acting Chief of Division of Chemistry, Hygienic Laboratory, from 1919-1920 (3, 4). Elvove, an immigrant success story who arrived in the US from Kiev (then in the Russian empire, now in Ukraine) at age 14, worked as an expert technician in the Laboratory since the time of Kastle. Later in his career, Elvove helped to solve the mystery of Jamaican ginger (Jake) poisoning, a serious public health problem during Prohibition, in collaboration with NIH pharmacologist Maurice Smith (3, 19). Owing to its high alcohol content (70%), drinking this elixir, sold in pharmacies for various medicinal purposes, was a convenient way to imbibe. In 1930 and 1931, adulterated preparations of Jake were identified as the source of widespread episodes of weakening and paralysis of extremities. In careful analytical work in 1931, Elvove and Smith identified tri-*ortho*-cresyl phosphate as the toxic diluting agent in impure Jake, primarily produced by one disreputable Boston firm (3, 20). Elvove later developed the most advanced method for measuring fluoride in drinking water to ± 0.1 ppm, which allowed dental surgeon H. Trendley Dean of NIH to establish fluoridation as a safe means of preventing dental caries (21).

In 1920 William Mansfield Clark (1884-1964), whose electrochemical measurements resulted in a correction of the Nernst equation, moved from the Department of Agriculture to the Hygienic Laboratory as Chief of the Division of Chemistry (9, 22). By 1925, following a major expansion in the previous 15 years, the Hygienic Laboratory employed 46 scientists and 71 support staff.

Thus, Clark saw a much broader scientific scope of work than previous Chiefs. The analytical work continued, supervised by Elvove, while Clark began pioneering research on oxidation-reduction systems using electrochemical and colorimetric indicators. He was known to emphasize accuracy in physicochemical measurements in order to draw mechanistic conclusions. Clark wrote a definitive book on acid-base chemistry, *The Determination of Hydrogen Ions* (1920) (23). An important part of the Division's work during this period was the study of the toxic effects of tetraethyl lead. Tetraethyl lead was used as an additive to gasoline starting in 1923 to reduce pre-ignition engine "knocking" and valve wear. Central to the research on its toxicology was the design of a temperature-controlled oven (previously unavailable) to burn human feces, an oven constructed mainly by Clark himself (3). Subsequent research revealed its toxicity, and its use as a gasoline additive was eventually phased out (4). Clark was a skilled glassblower and machinist and aided other researchers in the lab to build complicated equipment. According to Elvove, he could "make almost any desired piece of apparatus" and did so with "utmost friendliness and kindness" (3). In 1927, Clark was appointed Professor at Johns Hopkins University where he spent the remainder of his distinguished career.

The slow process of transforming the Hygienic Laboratory into the NIH began in the wake of World War I (7). Chemical weapons were introduced during the War, and US access to German-manufactured dyestuffs and other chemical products was prevented. Consequently, there was a growing public awareness of the importance of developing domestic chemical infrastructure, especially for solving health problems. During World War I, the Chemical Warfare Service of the War Department sought to establish a private institute to apply basic chemistry to medical problems. A concerted effort to create a US government institute for basic science studies, including chemistry, in a biomedical context was championed by Charles H. Herty, a former (1915-16) President of the American Chemical Society (ACS). There was a need to centralize and coordinate government health research and to broaden the existing legislation from utilitarian science to basic research, which at the time was mainly limited to academia and private institutes (7). However, US government support of basic research was highly controversial and opposed by powerful interests. Following extended unsuccessful efforts to obtain philanthropic support for their initiative in the 1920s, backers of expanded medical research enlisted the support of Senator Joseph Ransdell (Louisiana), who introduced a bill in 1926 that mandated

federal support for this research. This effort was aided by current influenza outbreaks. After overcoming political opposition and trimming its goals, this effort culminated in the passage of the Ransdell Act, signed into law on May 26, 1930, by President Hoover. This law renamed the Hygienic Laboratory as the National Institute (singular) of Health. The act stipulated that additional resources from both public and private funds (almost nonexistent by that time during the Depression era) would be provided to the new NIH. The Division of Chemistry at that time was still one of only four NIH divisions. The mission of NIH was defined as, "study, investigation and research in the fundamental problems of the diseases of man and matters pertaining thereto." The new mission included chronic diseases and indicated a shift away from the applied study of factors contributing to disease, especially infection. Fellowships for associate researchers were to be awarded, and President Hoover himself promised to help solicit private funding toward this goal (7, p 161). Even before this formal shift away from applied questions of environmental health risk, the Division of Chemistry was involved in fundamental chemical questions such as acid-base chemistry and oxidation-reduction reactions and carbohydrate chemistry, which had no obvious disease application. US Surgeon General Hugh Cummings commented that he did not know of any possible connection that basic research on carbohydrates in the Division of Chemistry would have to public health (7, p 168). Fortunately, the mission for NIH of conducting basic research to explore complex aspects of human disease, its causes and prevention, has been realized. Thus, the current successful model of investigator-initiated research projects has prevailed at NIH, especially during its post World War II expansion (24).

In 1937 the National Cancer Institute was formed by an act of Congress, and in 1944 it was designated as a division of NIH (7). The National Heart Act brought the National Heart Institute into NIH in 1948, making NIH plural (National Institutes of Health). Meanwhile, in 1935 Luke and Helen Wilson made an initial donation of 45 acres of their estate in Bethesda, MD, to the federal government to be used for the expansion of medical research. The new Bethesda NIH campus (now occupying 70 acres) was occupied between 1938 and 1941, and the Division moved there from Washington, DC (2). The Division of Chemistry was initially located in Building 4 (in 1940, along with Divisions of Pharmacology and Zoology), where it remained for 45 years.

In response to emerging health concerns along with advances in technology, reorganization and expansion of NIH followed. In 1948, the original divisions of the old National Institute of Health were divided into two newly created institutes: the National Microbiological Institute and the Experimental Biology and Medicine Institute (EBMI). EBMI was the administrative home of the former Division of Chemistry (since World War II known as LC). On August 15, 1950, President Harry S. Truman signed the Omnibus Medical Research Act into law (Public Law 81-692) establishing NIAMD within the Public Health Service. The new institute, NIAMD, incorporated the laboratories of the EBMI, including the Laboratory of Chemistry. Thus, 1950 marked the birth of NIAMD, an event celebrated in 2010 with a symposium on NIDDK's 60th anniversary at the Fall National Meeting of the ACS (Division of Medicinal Chemistry). As Congress responded to shifting emphases on health problems, several name changes ensued that corresponded to the addition of new centers and/or the creation of new institutes. Thus, the Institute name was changed from NIAMD to NIAMDD (addition of digestive diseases, 1972), to NIADDK (addition of diabetes and kidney diseases, 1981) and then to NIDDK (removal of arthritis through formation of a new and separate institute of arthritis and neuromuscular diseases, NIAMS, 1986).

Reorganization of Chemistry Labs and Formation of LBC and LMC

Before a description of current and recent individual research programs and highlights, it is useful to briefly discuss the administrative adjustments to the laboratories that were primarily responsible for organic chemistry in the institute. LBC as it now exists was formed by a process of "mitosis" and "meiosis." In 1978, John W. Daly (1933-2008, Figure 3 (lower)), originally in LC under Bernhard Witkop (1917-2010) as Chief (25), was appointed Chief of the newly created offshoot, LBC. At its beginning LBC consisted of Daly's Section on Pharmacodynamics, a Section on Oxidation Mechanisms headed by Don Jerina (1940-2011), and Phil Skolnick's Section on Neuroscience. In 1985, LC was divided into two labs, consisting of LMC and the sections remaining in LC with Witkop as Chief. In 1985, the LC moved to a refurbished Building 8, where LBC is currently located.



Figure 3. Organic chemists of the Laboratory in the lab and at leisure. Upper: Elias Elvove, seated at laboratory bench, Division of Chemistry, ca. 1938. (photo NIH Office of History, <http://ihm.nlm.nih.gov/images/B06647>). Lower: From left: Tom Spande, Neil Glaudemans, John W. Daly and Cyrus R. Creveling of NIDDK at the 65th Birthday Symposium in Honor of John Daly, held in Bethesda in 1998 (photo NIH Medical Arts and Photography Branch).

After Witkop retired in 1985, the Scientific Director of the NIDDK Intramural Research Program orchestrated a complex series of reorganizations of the chemistry groups. Cornelis P. J. (Neil) Glaudemans, a carbohydrate chemist, was appointed Chief of LC and served from 1985 until 1988. The Laboratory of Analytical Chemistry (LAC) was created during that period with David F. Johnson (1932-2007), who pioneered techniques in steroid chromatography, as Chief. In 1988, the Sections remaining in LC were merged into LBC, with Daly as Chief (26), and LC ceased to exist formally. A separate Laboratory of Neuroscience (LN) had been excised from LBC in 1987 with Skolnick as Chief. At that time, Kenner Rice's group moved from LC to LN, and Rice became Chief of the Section on Drug Design and Synthesis. In 1989 Rice formed his own Laboratory (LMC, existing

until 2006) and served as Chief. LMC consisted of Rice's Section on Drug Design and Synthesis and two other sections that had belonged to LC: Carbohydrates (Glaudemans) and Biomedical Chemistry (Paul Torrence). Rice's Section continued the work on drugs of abuse begun in LC by Lyndon F. Small (1897-1957) (27). The staff of LAC was merged into LBC in 1996. When Daly retired in 1998, Kenneth L. Kirk was appointed Chief, LBC, and upon his retirement in 2008, Kenneth A. Jacobson was appointed and is the current Chief of LBC.

Bridging to the Present—Topical Summary

The discussion of the research highlights that follows will be placed to some extent in the context of the organizational changes but, as a whole, should be considered a brief historical record of chemistry in LBC/LC/LMC, i.e. from the standpoint of the underlying science, not administrative moves.

Carbohydrate Research

Carbohydrate research formed one of the connecting links from the Division of Chemistry, Hygienic Laboratory, to the LC, NIAMD. Claude S. Hudson (1881-1952), who served as Chief of the Division of Chemistry from 1928 to January 31, 1951. In January 1929, the Division of Chemistry consisted of a scientific staff of 13 (including Hudson and two Fellows) (28), which increased to 15 by July 1936. Hudson served first in the Hygienic Lab and then at NIH, and was "present at the creation" of NIAMD (4, 5). He also embodied the central role of organic chemistry in the early days of NIAMD, although his Ph.D. was in physics. Prior to joining the Hygienic Lab in 1928 Hudson held positions in academia and in various Governmental agencies, including the National Bureau of Standards, War Department and the Department of Agriculture. During his tenure as Chief of the Division of Chemistry, Hudson did fundamental work on the chemistry of carbohydrates, which as food components fit the theme of the Hygienic Lab. However, Hudson went far beyond that context and mounted a large effort devoted to fundamental studies of sugars. He used carbohydrates to examine van't Hoff's hypothesis on the additive nature of optical rotatory power and explored the mechanism of mutarotation of sugars (4,5). Hudson's Lactone Rule correlates the sign of the optical rotation of aldonic acid lactones with the configuration of that carbon atom whose hydroxyl group forms the lactone. His success led to the premier research award of the Carbohydrate Division of the ACS being named after him. Hudson considered his years in the Division of Chemistry his most productive

and happy ones (4). There are many colorful anecdotes about Hudson (known as “Huddy”), for example, when his assistant failed to save a few seed crystals of a desired product for later use in crystallization, Hudson wandered for days and was heard muttering “he threw away his bait.” Another story is that Hudson figuratively existed as either of two “enantiomers” (mirror images): a party-loving “levorotatory” persona that lived life to the fullest and a serious minded “dextrorotatory” one that demanded meticulousness in the lab.

Hudson’s paper on xylitol derivatives in early 1944 reflected the name change from the Division of Chemistry to the Chemistry Laboratory (29). In October 1948, the Chemistry Laboratory was renamed the Laboratory of Chemistry and Chemotherapy under Hudson’s leadership with Small as the Assistant Chief (30). When Hudson retired as Chief of the Laboratory and Section on Carbohydrates in early 1951, Small became Chief of the renamed Laboratory of Chemistry, and Hewitt Grenville Fletcher Jr. (1917-1973) was appointed Chief of the Section (31). Fletcher and his group began a strong synthetic program in carbohydrate synthesis, especially focusing on the synthesis of riboses, deoxyriboses, acetamido sugars, and especially the potent anti-viral nucleoside “ara-A” (32), now a widely used anti-HIV drug. Fletcher continued his research work until his death. Outside the lab, he and his successor, Glaudemans, were also known for their sailing activities.

In 1973 Glaudemans succeeded Fletcher as Chief of the Carbohydrate Section in LC and initiated a comprehensive study of the interactions of antibodies with bacterial polysaccharide antigens (33). This work was facilitated by the advent of monoclonal antibodies. Employing the use of synthetic unnatural sugar-containing derivatives (such as a series of fluoro-deoxy galactoses), Glaudemans and Paul Kovac and others in the group were able to construct models of binding sites for oligosaccharides, dextran and a number of bacterial polysaccharides with a series of monoclonal antibodies.

Glaudemans retired in 1998, and Kovac became Chief of the Section, which at the time was under LMC. He and his group have expanded this work to the construction of conjugate vaccines from synthetic fragments that mimic the structures of bacterial carbohydrate antigens such as those of cholera and anthrax (34, 35). The long-term goal is to develop conjugate vaccines from synthetic oligosaccharides that can provide lasting immunity from infectious bacterial diseases (34). Exploratory work in this area led to the discovery (35) that antigenic lipopolysaccharides can be directly conjugated to carrier

proteins using squaric acid chemistry, which simplifies industrial vaccine production.

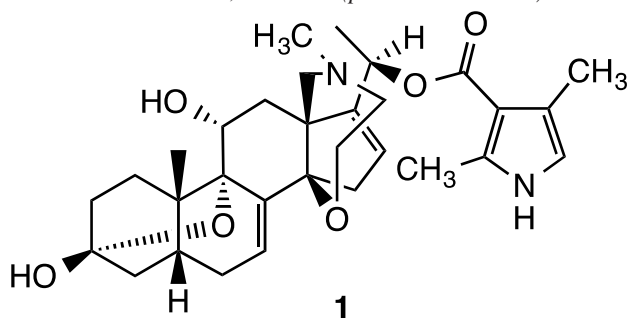
Natural Products

Witkop was trained at the University of Munich with a Ph.D. thesis on toxin chemistry and in 1944 was forced to retreat to a farm refuge in Southern Germany, eventually arriving in the US in 1947 to continue research work at Harvard (36). He began work at NIH in 1950, was appointed Chief of LC, NIAMD, in 1957 and served until 1988 (25). His influence and contributions to organic chemistry in NIDDK were profound, not just in the science, but also in his influence on a younger generation of scientists, both American and from foreign lands, in particular from Japan. His research group published roughly 400 papers on diverse aspects of synthetic chemistry, photochemistry, reaction mechanisms, and natural products.

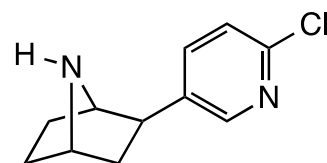
In 1962, Witkop sent a visiting fellow, Fritz Märki, to Colombia to check out stories of the Colombian poison dart frog *Phyllobates aurotaenia*, an excellent example of curiosity-driven research. This expedition, which included biologist Marta Latham, confirmed the potent biological activity of extracts. The group undertook in the field preliminary characterization that identified the active principles as a steroidal alkaloid, but lacked sufficient quantity for further structural characterization. Witkop enlisted Daly to go with Latham on a subsequent expedition. This and later trips netted 2400 frogs that yielded a total of 30 mg of material from which several toxic alkaloids were isolated. Subsequent work by Daly, and an X-ray structure by Isabella Karle of a crystalline derivative prepared by Takashi Tokuyama (Figure 4), led to the characterization of the main neurotoxin, which was given the name batrachotoxin (BTX, **1**, from the Greek word “batrachos,” meaning frog) by Witkop. BTX is used widely as a research probe (37). This alkaloid as the most potent nonpeptidal toxin proved to be one of the most poisonous organic substances known, with an LD₅₀ in mice of 2 µg/kg. In 1971, Edson Albuquerque of University of Maryland confirmed and extended Märki’s observations to conclude that sodium channels are the site of action of BTX (38). Thus, this toxic principle of the poison dart frog was shown to cause an irreversible increase in the permeability of electrically excitable membranes to sodium ions.



Figure 4. Bernhard Witkop, John Daly and Takashi Tokuyama (left to right) examining the structure of batrachotoxin, ca. 1969. (photo NIH Record).



The results of these expeditions had a major impact on the course of research in LC. Thus, the discovery of BTX launched a 40-year research program at NIH on frog alkaloids that led to extremely important uses of BTX and other toxins in a host of research applications. Daly, frequently accompanied by his long-time associate Charles Myers of the American Museum of Natural History, made numerous trips to rain forests and other locales where exotic species of amphibians could be found and he collected an enormous inventory of skin extracts (26). Assisted by skilled coworkers, most recently by Tom Spande, Martin Garraffo, and Noel Whittaker, these were analyzed by increasingly sensitive mass spectrometry, chromatographic and NMR techniques, and led to the isolation and characterization of approximately 1000 alkaloids with potent and useful activities. Included are epibatadine (2), pumiliotoxins and many bicyclic “izidines” (39). The studies of the pharmacological profiles of these compounds, as well as refinements of analytical techniques and development of valuable microsynthetic methods, produced a wealth of scientific dividends.



2

A fascinating aspect of this story involved the biosynthesis of these alkaloids. All attempts to entice frogs held in captivity to produce alkaloids proved futile. Measures tested for increasing toxin production included scaring frogs with natural predator snakes. The recognition of sequestration of alkaloids from dietary arthropods came only recently, a discovery by the Daly group that expanded the concept of his program of bioprospecting. Daly’s energetic efforts continued unabated until his death in 2008. Valuable samples of extracts remain to be examined, a task left to Daly’s close academic colleagues Richard Fitch, Ralph A. Saporito, and Tappy H. Jones, as well as others carrying on similar work. Aspects of this work were recently reviewed in a memorial tribute to Daly published in a special issue of *Heterocycles* (40).

The talent available to sustain a strong natural products research program remains in LBC. Carole Bewley, Chief, Section on Natural Products, joined the laboratory in 2000 and is using natural products chemistry to identify new treatments of viral, bacterial, and neoplastic diseases. Trained in the area of marine natural products, Bewley has targeted medical problems of profound significance, including tuberculosis and HIV infection, taking advantage of the vast universe of naturally occurring compounds that possess potent biological activities. Such compounds, when identified, are used as leads that, with chemical modification, can be converted to organic structures with improved pharmacological properties. For example, starting from marine invertebrates, Bewley and her group have identified several classes of novel marine natural products, also known as secondary metabolites, which potentially inhibit HIV-1 infection and tumor cell growth *in vitro*. Results from these multi-faceted studies of biologically active natural products, many of which are collected from marine origins, include the discovery and full characterization of novel carbohydrate binding proteins and enzyme inhibitors from understudied sources and chemical libraries. Novel inhibitors such as the anabaenapeptins, potent protease inhibitors, and the chrysphaentins, which kill multiple strains of drug-resistant bacteria, have resulted from these efforts (41, 42).

Organic Synthesis and Organic Mechanisms

Research in organic synthesis and mechanisms from the 1960s through the 1990s touched on topics as fundamental and diverse as the NIH shift, peptide chemistry, physical organic studies of conformation in catalysis and fluorine in bioorganic chemistry. These investigations are outlined below.

The story of the NIH shift and oxidation mechanisms provides an excellent example of discovery-driven research. In the 1960s, attempts to use isotopic labeling to measure the rate of enzymatically catalyzed oxidation of 4-tritio-phenylalanine were thwarted by unexpected isotope retention in the tyrosine product. A mechanism involving arene oxides was proposed and the ensuing rearrangement termed “the NIH Shift,” a transfer of an aromatic hydrogen atom to a neighboring ring position during ring hydroxylation, received much support in subsequent research (43). The discovery of this process, confirmed in many subsequent experiments, was particularly important in the study of the chemistry and biochemistry of these arene oxides that are formed during the oxidative metabolism of aromatic compounds, most notably polycyclic aromatic hydrocarbons (PAH). For example, the mechanistic details of the NIH shift provided a basis for explaining why certain PAHs (present in chimney soot and bus exhaust) are highly carcinogenic and others are less so. The impressive research of Jerina and his Section on Oxidation Mechanisms in LBC, NIDDK, dramatically attested to the importance of this seminal discovery by Daly, Witkop, Gordon Guroff (1933-1999), Sidney Udenfriend (1918-2001) and others at NIH (44). In 1990, Jerina was described as a prospective Chemistry Nobel Prize winner based on his citation record for work on the role of arene oxides in carcinogenesis and drug metabolism (45).

LC occupied a critical position in biomedical research at NIH as the biological sciences revealed the increasing complexities of structure and functions of biomolecules such as amino acids and peptides. Critical to progress was an in-depth understanding of the physical organic principles involved in interactions of small molecules with macromolecular systems. In addition, having available in the Institute the knowledge and experience of practitioners of modern chemistry proved to be a valuable resource for other disciplines. Important contributions included the discovery by Witkop and Erhard Gross (1928-1981) that cyanogen bromide can selectively cleave peptide bonds at the carbonyl group

of a methionine residue (46). This breakthrough in protein chemistry facilitated enormous contributions to this field, playing a part in the syntheses of hormones such as somatostatin (47). Thus, bacteria were engineered to produce somatostatin linked to galactosidase through a methionine residue. Cyanogen bromide cleaved the methionine linkage releasing somatostatin, thus completing a recombinant DNA strategy wherein a bacterium produced a polypeptide of higher organisms. A similar approach using cyanogen bromide cleavage was used in an industrial synthesis of insulin.

Witkop's extensive work in tryptophan chemistry provides another example of the application of fundamental organic chemistry to important biological systems (48), including studies of indolenine hydroperoxide intermediates involved in tryptophan oxidation to *N*-formyl kynurenines, and a novel photochemical cyclization of chloroacetyl derivatives to produce tricyclic indole derivatives. These and other studies during this period were typical of the applications of organic chemistry to understanding the fundamental chemical behavior of biological building blocks.

Another important discovery in the 1960s provided valuable tools for neuropharmacology. The false neurotransmitter 6-hydroxydopamine, discovered by Witkop and Siro Senoh (the first NIH visiting scientist from Japan) in 1959, was found to be selectively toxic to dopaminergic neurons. This chemical sympathectomy had many applications including implications for the etiology of Parkinson's disease. Daly and Cyrus R. Creveling (1930-2008) later observed similar neurotoxicity of hydroxyserotonin derivatives on serotonergic neurons (49).

Perhaps no chemist in the laboratory was as attuned to physical organic principles as was Louis A. Cohen (1926-1996), who came to LC in 1954. He thrived on the applications of physical organic constants, especially to enzyme catalysis. In his research, he often attempted to mimic nature by the clever design of “test-tube” reactions. For example, in the 1970s and 1980s he designed compounds predicted to exist in favored conformations for lactone formation based on a “trimethyl” lock (50). This concept of “stereopopulation control” indeed produced model reactions with rate enhancements approaching that of enzyme catalysis. Much of this work was done with postdoctoral fellows Sheldon Milstien and Ronald T. Borchardt (50, 51). He also pioneered with postdoctoral fellow Leon Farber the electrochemical cleavage of proteins at tyrosine residues (52). His knowledge of

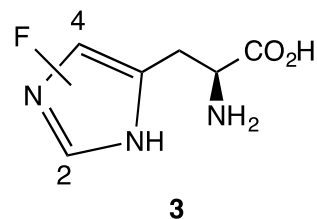
physical organic principles was a valuable resource that was used by many scientists in NIDDK and throughout NIH until his death in 1996.

Fluorinated small molecules have achieved wide use in biomedical research, particularly in the design of drugs, biochemical probes and biological tracers. In this regard, the number of medicinal agents that contain fluorine substituents is disproportionately high relative to other halogens and other functional groups. The special properties of fluorine, specifically its small size and high electronegativity, are largely responsible for its importance in biomedical research. There have been several notable contributions by NIDDK chemists to this area.

One such area is in fluorinated amino acids. (*S*)-Proline plays important and unique roles in protein structure because of its conformational rigidity. For example proline and (*2S,4R*)-4-hydroxyproline are critical components of collagen, and have been powerful tools in the study of the special properties of proline-containing peptides and proteins. In 1965 the first syntheses of (*2S,4R*)-4-fluoroproline and (*2S,4S*)-4-fluoroproline were reported by Witkop and co-workers in LC (53), which were used to study collagen biosynthesis. Subsequent work in several groups demonstrated the effectiveness of using fluorinated proline derivatives to study the many important roles of proline in protein structure and function.

(*S*)-Histidine also has many roles in biological structure and function. Histidine is often present in the active site of enzymes where both of the basic nitrogens of the imidazole ring have important functional roles. Hydrogen-bonding of the imidazole ring can also play important structural roles in proteins. In addition, histidine serves as the biological precursor of histamine, an important player in the immune response that also serves as a neurotransmitter. In the mid 1960s, Cohen initiated attempts to synthesize fluorinated imidazole derivatives, including histidine and histamine, recognizing that the strong electronegative effects of fluorine could evoke profound changes in biological and chemical behavior. Success in this endeavor hinged on the discovery of a new fluorination procedure and in 1969, Kirk and Cohen reported the synthesis of several ring-fluorinated imidazole derivatives using their newly developed photochemical Schiemann reaction of diazonium fluoroborates (54). This breakthrough opened the door to a myriad of research projects utilizing the unique chemical and biochemical properties of fluorinated imidazoles,

in particular 2- and 4-fluoro-(*S*)-histidine (**3**). Use of these analogues to study protein structure and function continues to this day (55).



In the 1980s, in collaboration with Daly and Creveling, Kirk and his group extended the study of fluorinated analogues to include fluorinated derivatives of biogenic amines: norepinephrine, epinephrine and related adrenergic agonists (56). Fluorine-induced selectivities towards α - or β -adrenergic receptors, depending on the site of fluorination, resulted in a broad program of synthesis and pharmacology, both to exploit these selectivities, and to attempt to determine the mechanism(s) by which fluorine exerted such a profound influence.

Subsequently the related fluorinated amino acids, viz. fluorinated 3,4-dihydroxyphenylalanine (FDOPA) and 3,4-dihydroxyphenylserine (FDOPS), were synthesized. These analogues proved to be very important in a variety of projects, especially ^{18}F -labelled analogues as agents for *in vivo* imaging of the heart and brain using positron emission tomography (PET). Particularly in the 1980s and 1990s, the Kirk research group worked closely with the PET Department of the NIH Clinical Center in developing standard metabolites of 6-FDOPA that proved critical in the implementation of [^{18}F]6-FDOPA as a biological tracer (57).

Medicinal Chemistry

World War II brought a need to secure reliable sources of anti-malarial agents. Small was asked in 1938 by Rolla E. Dyer, Director of NIH, to refocus research efforts from his opiate program in the Division of Chemistry's Section on Chemotherapy (58) to seek synthetic antimalarials in anticipation of coming wartime quinine shortages (26). He and some of his group, including Erich Mosettig (1898-1964), moved from the University of Virginia to NIH (Division of Chemotherapy in DC) in 1939 where they began work on antimalarials. Mosettig was trained in Vienna, recruited from Ernest Spaeth's laboratory by Small and later became Chief of the Steroids Section, LC (59). Small's laboratory was one component of the Office of Scientific Research and Development (OSRD) antimalarial effort, and at the end of the war Small returned to his opiate program. In

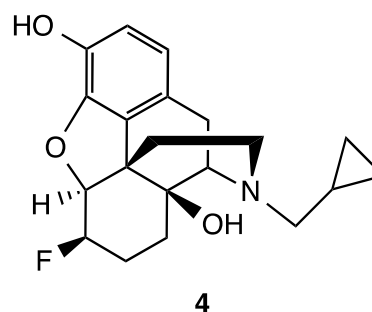
1948 the group was attached to Hudson's laboratory in Building 4 in Bethesda (30).

Small was asked to concentrate on finding morphine and codeine replacements. Witkop's report (5) and the 1979 Smisson Award address given by Everette L. May (1914-2008) (60) describe these events in more detail. Rice's review of analgesic research at NIH (61) and a review by May and Arthur Jacobson (62) also provide considerable insight. May joined the group of Small and Mosettig in 1941, and became Chief of the Medicinal Chemistry Section in LC in 1960, where he remained until joining the faculty of Virginia Commonwealth University in 1977. Small succeeded Hudson as Chief of LC in 1951 and served until his death in 1957. Small was elected to the National Academy of Sciences in 1941, was recipient of the Hillebrand Prize of the Chemical Society of Washington in 1949, and was Editor of the *Journal of Organic Chemistry* for 13 years (1938-1951). Included in the list of important players in medicinal chemistry at this time were Arnold R. Brossi (1923-2011), who came from Hoffman LaRoche, and Rice, who began his NIDDK career in 1972 with Ulrich Weiss (1908-1992) and then as a fellow in May's section, and went on to become the Chief of the LMC.

NIDDK has been and continues to be a leading center of medicinal chemical research at NIH. Within this Institute there have been recent major efforts in the exploration of toxins that act at ion channels, receptors for drugs of abuse, biogenic amines, carbohydrates, purine receptors, and other classes of bioactive molecules. Representative examples of contributions to medicinal chemistry made by NIDDK chemists in the areas of opiates, purines, and nucleic acids are summarized briefly below.

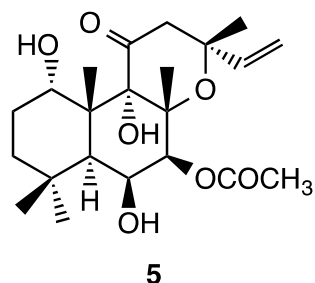
For decades LMC and its predecessors produced leading work in the medicinal chemistry of drugs of abuse (61). This laboratory inherited the role of the chemical research effort at the University of Virginia on opioids initiated in 1929 by the National Research Council of the National Academy of Sciences (62). Small's extensive work in the morphine alkaloids provided the foundation of modern structure activity relationship (SAR) in the opiate series and largely defined the chemical character of opiate reactivity. His discovery of metopon validated the program hypothesis that it was possible to separate the beneficial from the detrimental effects of morphine derivatives by chemical modification of the structure. This work provided the proof of principle for the program that still permeates contemporary analgesic research. May explored the SAR of many classes of opioid analgesics,

including the 6,7-benzomorphans and the 5-phenylmorphans (60). He developed the synthetic opiate analgesics phenazocine and levo-alpha-acetylmethadol, which have been used clinically. He also introduced an antimalarial bromophenanthrene methanol, which was used as a life-saving treatment during the Vietnam War. The analgesic Talwin still in use today was developed as a direct result of May's discovery of the benzomorphans as analgesics.



Rice developed Cyclofoxy (4), a narcotic antagonist labeled with ^{18}F as a PET imaging agent for opioid receptors. Cyclofoxy was the first PET ligand that was designed on paper, synthesized, and studied in preclinical pharmacology and toxicology and introduced in humans all at a single institution, namely NIH (63). He and his associates published the first images of opioid receptor occupancy in a living primate in 1984 (63). Rice also developed the first practical total synthesis of opium products in 1980 (64). This methodology offers independence from foreign sources of opium, and such independence would enable opium poppy eradication as a strategy to eliminate heroin abuse. In 2006, Rice moved his program from NIDDK (30) to the National Institute on Drug Abuse (NIDA) (61) where it is now the Chemical Biology Research Branch.

As described above, John Daly made ground-breaking discoveries in the area of natural products isolation and characterization. In addition, in work closely related to his research in natural products, he earned acclaim in areas that included the investigation of the SARs for agonists/antagonists at adenosine, adrenergic, histamine, serotonin, and acetylcholine receptors. His pioneering research included studies on the modulation and functional relationships for systems involving calcium, cyclic nucleotides, ion channels and phospholipids. Two of the most important and widely used pharmacological probes introduced by Daly and coworkers were the activator of adenylate cyclase forskolin (5) and nicotinic acetylcholine receptor agonist epibatidine (2), which has spurred much research in new treatments for pain and dementia.



Daly's seminal studies on the mechanism of actions of caffeine and other xanthines, research that defined adenosine receptors as an important target for drug discovery, exemplified his ability to merge organic chemistry with pharmacology. His systematic work characterized the effects of adenosine analogues on cyclic AMP in the brain. These effects that were antagonized by methylxanthines established the concept of adenosine receptors in the brain. He also played a decisive role in establishing these receptors as *bona fide* biochemical entities and contributed to the discovery of receptor heterogeneity (65).

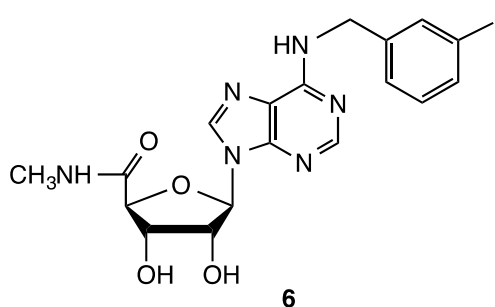
This research on adenosine receptors was facilitated greatly by Daly's development of a technique for prelabeling ATP in brain slices that allowed direct measurement of the conversion of the radiolabeled ATP into labeled cyclic AMP (66). Thus, one of the most efficient stimulators of cyclic AMP accumulation in brain slices proved to be adenosine. Extended studies revealed that cyclic AMP accumulation was antagonized by theophylline and other methylxanthines. It was enhanced by dipyridamole and papaverine, phosphodiesterase inhibitors that also prevent adenosine uptake into cells and thereby increase effective extracellular adenosine concentrations. Subsequent preparation of a series of analogues by Daly and his group helped to establish the fundamental SARs for these biologically important receptors (67).

K. Jacobson greatly extended research on adenosine receptors in particular, and on purinergic receptors in general. For example, he has explored SARs to introduce many widely-used ligand probes for the pharmacological study of GPCRs, e.g., the four adenosine receptors and eight P2Y receptors, which respond to extracellular nucleotides. These compounds have been essential in countless biological studies that are furthering delineation of the physiological role of extracellular purines as transmitters and modulators, particularly those actions mediated by GPCRs. Thirty seven compounds, including selective radioligands, designed and synthesized by Jacobson and his group are currently available from commercial sources as research tools. These ligands, most of which became available during the past decade, have had

a clear influence on the course of industrial and academic medicinal chemistry of purine receptors. For example, the discovery of the first A_{2B} adenosine receptor-selective antagonist in LBC has led to new preclinical candidates for treatment of asthma and diabetes later under development by several pharmaceutical companies (68).

Early in the studies of purine receptors at NIDDK, the potential value of structural exploration of these elusive proteins in drug design was recognized. Soon after cloning of the receptors in 1990, Jacobson and his group began molecular modeling of the adenosine receptors and their putative binding sites for agonists and antagonists. The computational probing of the architecture of purine and pyrimidine receptors was supported by site-directed mutagenesis. These structural insights, gained initially by using the relatively primitive modeling techniques available at the time were refined in stages by Jacobson and colleagues and have successfully guided ligand design. The recent determination of the X-ray structure of an agonist-bound A_{2A} adenosine receptor (69), which is a target for neurodegenerative diseases and inflammation, validated much of the preceding modeling work carried out in Jacobson's lab.

Basic research labs in the NIH can partner with pharmaceutical industry through a formal collaborative research and development agreement (CRADA). The ongoing program in LBC to develop selective adenosine receptor agonists has led to clinical trials of two adenosine receptor agonists originally synthesized by Jacobson in 1993, including the A_3 receptor-selective agonist IB-MECA (6). From 2006 to 2010, a CRADA was established with Can-Fite Biopharma to advance understanding of the therapeutic benefits of A_3 adenosine receptor agonists, which they promoted to clinical trials. These ongoing Phase II/III trials target inflammatory diseases such as rheumatoid arthritis, psoriasis and dry-eye disease and also liver cancer (70). IB-MECA and its 2-chloro analogue have been found to be well-tolerated in humans with promise as a broad based treatment for many chronic diseases.



Jürgen Wess is a pharmacologist and Chief of the Molecular Signaling Section of LBC. He has made seminal contributions to GPCR structure and function, particularly with respect to the muscarinic acetylcholine receptors (71).

Application of organic chemistry in the nucleic acid field has received considerable attention in NIDDK. Torrence, who served as Chief of the Biomedical Chemistry Section in the LAC of NIDDK from 1989 to 1999, carried out research in drug discovery for a variety of viral diseases. As part of this research, he studied the use of oligonucleotides, in particular based on the 2',5'-oligoadenylate system, as potential antiviral therapeutics (72). In 1999, Torrence joined the faculty of Northern Arizona University as chair of the chemistry department where he continued research into antiviral therapeutics until his retirement.

Dan Appella, who joined LBC in 2005, is exploring new types of synthetic peptide nucleic acids (PNAs) and small molecules with unique biomedical applications. PNAs hybridize with natural nucleic acids and are stable to enzymes that degrade DNA and RNA. Key design features of the Appella PNAs are the incorporation of cyclopentyl and lysine moieties that impart greater stability to the hybridized structures as well as a chemical handle to build complex, multivalent structures at the nanometer scale (73). In other work, the Appella group is developing new classes of small molecules with anti-HIV and anti-cancer activities that interact with biological targets considered to be challenging for traditional methods of drug development. The goal of this work is to develop new types of therapeutic compounds that take advantage of unique mechanisms of action.

Acknowledgments

Regarding the research summaries, it would be impossible to give appropriate credit to all of the chemists that have contributed to the success of research in NIDDK. In particular, the invaluable contributions of countless postdoctoral fellows and students are only embedded in the summaries we have provided, and not specifically cited. Indeed, our research in NIDDK is driven by these young colleagues who come to NIDDK to further their training in chemistry, but who bring with them fresh energy and ideas. In general, space and time have limited us in our coverage of past and present research. We have used two main sources of information

for the summary of early events. The first is an unpublished document composed by Elias Elvove in 1953, and we thank Paul Kovac who had been entrusted with this manuscript, for making it available to us. We also thank Kenner Rice and Tom Spande (NIDA) for helpful discussion. We acknowledge support from the Intramural Research Program of NIDDK, NIH, Bethesda, MD.

Supplemental Material

Page images of Ref. 3, an unpublished report by Elias Elvove, "History of the Laboratory of Chemistry from its Inception as the Division of Chemistry, Hygienic Laboratory, US Public Health Service, June 20, 1905, through the administration of Claude S. Hudson, 1950," can be found in the Supplemental Material for the *Bulletin for the History of Chemistry* at the journal's website, www.scs.uiuc.edu/~mainzv/HIST/bulletin/index.php.

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BOOK REVIEWS

Characters in Chemistry: A Celebration of the Humanity of Chemistry, Gary D. Patterson and Seth C. Rasmussen, Eds., ACS Symposium Series 1136, Washington, DC, American Chemical Society (distributed by Oxford University Press), 2013, xiii+248 pp, ISBN: 978-08412-2800-9) \$150 (hardback; e-book also available).

There seems to be general agreement among the authors of these chapters that a true chemical character is an individual who has made significant historical contributions to the science of chemistry and also had unusual personal traits that have made him or her stand out. The various chapters in this book cover a variety of chemical characters, ranging from the well-known, such as Bunsen, Crookes, and Davy, to the less familiar, like Yegor Vagner and George Rosenkranz. Not all of the individuals described in the book fulfill both of these qualifications, and, indeed, two of the chapters focus on topics that do not strictly correspond to either criterion. None the less, the overall result is a very readable and interesting excursion through the history of chemistry.

As described by William Jensen, Robert Bunsen certainly qualifies as having made many important contributions and also having had a rich personal history. In fact, there are so many Bunsen anecdotes that they are given a special classification as *Bunseniana*. The two observations about Bunsen that resonated most strongly with this reviewer are that the skin on his hands was so thick that he could take the cover off a hot crucible without using tongs, and that his official residence at Heidelberg was large enough so that he could set aside a separate room for his unwanted mail. Readers who have either burned their fingers from picking up a hot crucible lid or found that their office was not big enough for all

the papers they wanted to store will probably sympathize with these choices.

There is much less anecdotal material available about the next chemist who is profiled in this book. Joseph Black, the Scottish chemist who is best known as the discoverer of carbon dioxide, left surprisingly little personal information despite his rather long and distinguished career. Black was a popular teacher, an effective consultant to industries, and seems to have been very active socially. A significant number of his letters have recently been published, but these deal mainly with scientific and technical matters, giving little impression of his personal life. Robert Anderson, who wrote the chapter on Black, concludes that, “. . . Black as a person remains something of an enigma.”

Alan Rocke emphasizes the diversity of those who have contributed to chemistry by contrasting the lives of John Dalton and Humphry Davy. Dalton was a Quaker from a small town who believed in the plain life, whereas Davy aspired to the life of a London aristocrat. The two men were also poles apart philosophically, with Dalton as the traditional Enlightenment realist, and Davy, who was twelve years younger, being more of a Romantic who wrote poetry in his spare time. Seth Rasmussen focuses his chapter specifically on the early years when Davy was investigating the properties of gases. Gilbert and Sullivan fans will probably appreciate the fact that Davy was born and raised in Penzance, home of the famous Gilbert and Sullivan pirates. Like the Modern Major General in that play, Davy seems to have made himself an expert on many things without much formal training. As Rasmussen points out, “The greatest discoveries are not always made by the most highly trained or highly educated people.” On the other hand, many chemists

may be stunned to learn the extent to which Davy chose to experiment on himself by breathing various toxic gases for significant lengths of time, so much so that he became addicted to nitrous oxide. Davy was very lucky that he lived long enough to have such a distinguished career, so perhaps luck can be as important as training.

William Brock argues that Sir William Crookes personified the definition of the term chemical character in that he not only made significant contributions to chemistry but also had an unusual personality. Crookes had little formal training and did not make his career in either industry or an academic institution but instead made his living mainly as a scientific journalist. Despite this he was an innovator in many fields, including photography, chemistry, physics, agricultural science, and public health. Crookes was a keen observer and developed many scientific breakthroughs, such as the Crookes tube and the radiometer, from his observation of anomalies that apparently escaped the attention of others. His most unusual personality trait was his strong belief in spiritualism. His commitment was so strong that some of his critics said that it was as though he had two different personalities, one a rational scientist and the other a gullible believer in miracles.

Balazs and Istvan Hargittai tell the story of five Hungarian scientists, Theodore von Kármán, Leo Szilard, Eugene P. Wigner, John von Neumann, and Edward Teller, who emigrated to the United States before World War II to escape the persecution of the Jews by the Nazis. Each of them began their studies in chemistry, but later expanded to other disciplines; however, their chemistry background was very useful when they worked on the Manhattan Project to create the atomic bomb. In order to explain their unusual intellectual abilities and their strange accents the story spread that they were actually Martians, and the group happily adopted this label.

As far as this reviewer is concerned, my favorite Martian was Leo Szilard. According to one tale, Szilard was the origin of the story that the Hungarians were Martians. When Enrico Fermi was wondering why, if there were life on other planets, they had not made it to the Earth. Szilard replied that the Martians were already here; they were called Hungarians. Szilard's mind worked so fast that he often understood the meaning of other people's data before they had understood it themselves. In 1933, he was disgusted with the shortsightedness of Lord Rutherford's statement that the idea of obtaining energy on an industrial scale from the transformation of atoms was "moonshine." As he was going across the street near his London hotel he was suddenly struck with

the realization that it might be possible to use neutrons to create a nuclear chain reaction. This became the basis for the research that led to the atomic bomb. Later on, Szilard was one of the scientists who encouraged President Franklin Roosevelt to create the Manhattan Project.

George Rosenkranz was another chemist born in Hungary, although he was not part of the group of so-called Martians. He studied and worked initially in Zurich but later immigrated first to Cuba and then to Mexico to escape the Nazis. He achieved several breakthroughs in the field of steroid chemistry using Mexican plant sources as raw materials. James Traynham bases his chapter on a personal interview that he had with Rosenkranz. While in Zurich Rosenkranz supported himself by coaching a table-tennis team, performing in a theater troupe, and teaching people to play bridge. Bridge has always been his special passion. He has written 14 books on the subject and has been the national bridge champion of Mexico several times.

Gary Patterson describes Paul John Flory as yet a different kind of chemical character. Flory's scientific expertise is undisputed; he won the Nobel Prize in 1974 for his work in polymer chemistry. It is the other half of his qualifications that makes him an unusual character. For much of his professional life, Flory opposed violations of human rights, mainly in what was then the USSR. He worked to free scientists who had been imprisoned in Russia, opposed travel restrictions that the Soviets imposed on scientists, and helped individuals and their families immigrate to this country. As Patterson summarizes, "He was willing to risk his own life and reputation to support those who were persecuted or repressed."

David Lewis reports on the special contributions of Yegor Yegorovich Vagner, who first proposed the correct structure of α -pinene in a series of articles beginning in 1867. Previously, nine different chemists had attempted to solve this structural problem, and so Vagner's contribution was especially important. Vagner's most unusual trait was his commitment to amateur theater, an interest that started when he was a child and continued throughout the rest of his life. While he was a student at the university in Kazan he was well known for not only his attendance at the theater but also for his performances in amateur productions and his willingness to criticize the professional productions that he attended regularly.

By no means is the book limited to those who fit the definition given in the first paragraph above. Cathy Cobb presents an informative chapter on those individuals suspected of using poisons during the Renaissance.

She describes the advantages and disadvantages of the various poisons available in considerable detail, and also evaluates the charges of using poison that have been brought against various figures of the time, including Lucrezia Borgia (possibly innocent) and Caterina de' Medici (more likely guilty). It was particularly impressive that the author not only sampled the odor of a piece of arsenic ore, but also trained her dog to find a piece of the ore in a pile of debris. This is the sort of behavior that might get her included in a future volume about characters in chemistry.

Carmen Giunta's chapter on chemists as characters in fiction will be particularly useful to teachers who wish to assign out-of-class readings to supplement the topics on their syllabus. He suggests several resources that catalogue chemists in fiction, including WorldCat and Lab Lit.com. If a teacher would consider adding some popular references to his or her reading list, an additional source would be the ACS Undergraduate Blog on the topic, "Who are your favorite fictional chemists?" (<http://acsundergrad.wordpress.com/2012/03/06/who-are-your-favorite-fictional-chemists-here-are-ours/>). Some teachers may look askance at this web site, since it includes Walter White, who is a well-known example of a chemist using his knowledge for evil purposes. Another possible supplement to the excellent information that Giunta offers

is the online article called *Literature and Chemistry* by Jay Labinger. (<https://www.its.caltech.edu/~bi/labinger/nontechpdfs/16chemlit.pdf>)

The history of chemistry is a fascinating field of study, and one of the reasons for this appeal is the diverse character of those who study chemistry. As this book demonstrates, chemistry has attracted poets, pacifists, amateur thespians, bridge masters, humanitarians, spiritualists, and yes, even poisoners. Perhaps equally important, those who have made important discoveries have included both scientists trained at the best institutions of their time as well as those who had little formal training. Patterson and Rasmussen urge teachers to celebrate this diversity so that young people thinking about making chemistry their career will better understand that there is potentially a place for them regardless of who they are. This is a powerful message which deserves to be heard. It is to be hoped that many chemistry teachers will be inspired by this book to enliven their classes by sharing some of these stories about the characters who are responsible for creating the field of chemistry.

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Toxic Airs: Body, Place, Planet in Historical Perspective, James Rodger Fleming and Ann Johnson, Eds., University of Pittsburgh Press, Pittsburgh, 2014, xiv + 284 pp, ISBN 978-0-822-96290-8, \$28.95.

Toxic Airs is a collection of essays that investigate a wealth of worries about "bad" airs. Ranging from medieval worries about witches' breath to contemporary concerns with the rising levels of carbon dioxide, the essays of this book reveal a persistent anxiety about and fascination with the air we breathe. As the editors explain, "Humans are, not surprisingly, threatened by compromises to their air, and they have reacted by wielding their full arsenal of understandings on toxic airs" (p ix).

Humans' many and varied reactions to compromised air are what motivate the book and will interest readers. Taken as a whole, this is not merely a catalog of aerial

concerns, but a full examination of how humans, in different times and places, have tried to address perceived problems with the air they breathe. Detailed case studies of tear gas, smog, acid rain, deadly airs, ozone, radiation, and automotive emissions reveal a wide range of attempts to contain or cope with compromised airs.

The majority of these cases are twentieth and twenty-first century issues, but there are three outlier chapters on earlier periods that deserve considerable attention because of the counterpoints they offer to contemporary studies. Brenda Gardenour Walter contributes an essay on the late medieval period that provides a useful overview of how longstanding medical traditions imbued airs with both natural and supernatural powers. Christopher Hamlin's close reading of Reginald Orton's discourse on cholera and deadly air yields a powerful insight for modern medicine and medical historians: that medicine should

consider the chemical qualities of environmental airs as well as microbes in searching for the causes of disease. James Rodger Fleming's chapter on the long and varied history of "carbon die-oxide" takes readers on a lively tour of the human fascination with CO₂ from ancient sites of prophecy and divinity through contemporary schemes for storing the gas. Taken together, these three chapters make an argument for thinking about the atmosphere and toxic airs in holistic terms over the *longue durée*, rather than considering atmospheric toxins as new and discrete problems, the more common approach of the twentieth and twenty-first centuries.

The reader will have to draw connections between the three articles mentioned above and the remaining nine, eight of which focus on how governments and politicians have reacted to specific air concerns since World War II. Scholars with interests in the interaction between the scientific community and governments will find many of these essays useful, as they mine the fruitful ground of science policy creation.

Some of these essays expose politicians and governments as tone deaf and slow to listen to the concerns of their publics. Historian Roger Eardley-Pryor tells an interesting and paradoxical story of how tear gas became safe for domestic policing while simultaneously considered inhumane in warfare. While the scientific community argued against tear gas as a gateway chemical weapon that would lead to the use of other, deadlier chemicals in international warfare, scientists and the federal government seemingly ignored the war that was starting in America's cities, where police departments regularly employed tear gas against the urban unrest and race riots of the 1960s. Anthropologist Susie Kilshaw turns to the victims of chemical weapons, focusing on Britain's Gulf War veterans and their health fears. Though soldiers may never have been exposed to chemical weapons—a point that bureaucrats and physicians often stress—memories of the constant chemical threat have strongly influenced how veterans understand their own health and environmental dangers.

When governments have responded against atmospheric threats, as in the history of automobile emissions control and the fight against smog, their actions have not yielded the desired results because regulatory methods have not kept pace with scientific discoveries. Victorian anti-smoke reformers understood that there was a linear relation between smoke production and increasing levels of air pollution, so they created a regulatory model that focused on controlling emissions. Chemist Peter Brimblecombe's chapter on the history of under-

standing photochemical smog explains how scientists working on Los Angeles's smog realized the limits of linear regulation. As they better understood the multiple sources of photochemical smog, scientists switched to urban monitoring networks, but policy makers remained locked in a regulatory model that targets primary emissions production. Similarly, the engineering history that Richard Chase Dunn and Ann Johnson have uncovered reveals how the linear understanding of emissions and air pollution hindered engineers in their goal of reducing pollution without reducing miles driven. This account dovetails nicely with Brimblecombe's, even as it reveals that engineers and chemists were not often in conversation as they worked on the same problem. Taken together, these chapters make excellent points about the need for flexible legislation and regulation to respond to modern atmospheric concerns.

If misunderstanding and miscommunication between scientists, engineers and politicians have hampered regulation, one might conclude that scientists should directly shape regulatory policy. Four case-studies of scientists as politicians and bureaucrats disprove this conclusion. Jongmin Lee, a scholar of science, technology, and society, contributes a chapter on the early efforts of the Environmental Protection Agency to combine epidemiological research and air quality monitoring. While this interrelated approach to health and environment made sense to scientists, it was hard to organize and slow to provide the evidence that Congress wanted from a regulatory agency. In historian E. Jerry Jessee's chapter on nuclear weapons testing and radioactive fallout, the divide between scientists within and outside of the Atomic Energy Commission—all of whom were doing atmospheric research—is vexed. The political imperative to test nuclear weapons led AEC scientists to present their research and suggestions differently from independent scientists. Historian Rachel Rothschild tells a similarly depressing story about international cooperation and the limits thereof in the history of acid rain. Despite the creation of an international organization for scientific collaboration in the 1960s, the political cultures of the different nations prohibited true and open cooperation to reduce acid rain. Historian Matthias Dörries considers the public debates about saving the ozone layer in the 1970s, which he characterizes as "a considerably more cooperative political environment than ... the nuclear winter debate of the 1980s or current climate change discussions" (p 209). Even in this relatively cooperative moment, the disagreements between scientists who favored modeling and those engaged in empirical research were deep and arrested action in many of the same ways

that early misunderstandings between scientists and politicians had. While uncertainty is a useful and necessary principle in science, these chapters reveal its limits for policy and regulation.

After a series of chapters that emphasize the miscommunications between scientists and politicians, Andrea Polli's exploration of how art can communicate science and policy to the public is refreshing. Polli, the artist behind *Particle Falls*, a real-time visualization of air quality data that has been displayed in San Jose, California, and Philadelphia, introduces readers to artists and artworks that directly raise questions about the state of the air. The many examples of productive collaborations between artists and scientists might not offer regulatory answers, but they provide hope for bringing public pres-

sure to demand action on air quality and climate change.

As editors, Fleming and Johnson had explicitly interdisciplinary goals of crossing temporal, geographic and disciplinary boundaries. While successful in assembling an interdisciplinary group of scholars, the editors might have done more to bring cohesion to the collection. The essays often operate on different registers—while they speak to similar issues, the authors rarely speak to one another. As a result, readers might pick up this collection for a single essay and fail to see a reason to read further, thereby missing the many valuable perspectives that the editors carefully assembled.

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The American Synthetic Chemicals Industry: War and Politics, 1910–1930, Kathryn Steen, The University of North Carolina Press, Chapel Hill, 2014, 418 pp, ISBN 978-1-4696-1290-4, \$39.95 paper.

In 1920, in the wake of World War I, a collective of chemical manufacturers urged the Senate Committee on Finance to maintain rigorous protections established during the war for their industries against potential German resurgence and encroachment (p 195):

The manufacturers testified that tariffs alone would be inadequate to protect their industry for the next several years. They knew that the German manufacturers still surpassed the Americans in chemical knowledge, research and experience, and they had to make the case that Americans, while not yet equal to the Germans, could catch up in a reasonable time-frame.

The chemistry—and chemical manufacture in question—was the aromatic organic chemistry of synthetic dyes and pharmaceuticals.

A decade later, the situation had changed profoundly. Although continued high tariffs (and wartime confiscation of patents) had insured a modest domestic success of US manufacturers of these products, resurgent German manufacturers “had recovered many of the international markets where Americans had ventured during the war.”

However, the American synthetic organic chemicals manufacturers had taken the industry in different directions, where “the Germans had little or no head start on American rivals, and the two sides competed with relative parity” (p 237, both quotations).

What Steen styles a “new ‘American’ industry” (e.g., p 280) consisted of a concatenation of new raw materials, new methods and new synthetic organic chemical products. The spectrum of new raw materials derived from petro-chemicals (among others). Regarding the new chemical products: these were now aliphatic (e.g. ethylene and its compounds) rather than aromatic. They were utilized to make commercial materials such as artificial fabrics, plastics and rubber, and were intended for different industries than the aromatic organic dyes, most notably the rapidly-developing automobile industry. New physical-chemical techniques, employing very high temperatures and pressures were deployed to create the products and they were mass produced. These changes of direction were attended by industrial innovations (or at least enhancements), notably, the development of in-house industrial research, the hiring of American academically trained chemists, the utilization of university chemists as consultants, and the ascendancy of chemical engineering. Particularly in her last chapter (chapter 8: An “American” Industry, 1919–1930), Steen traces these

developments in each of the largest organic chemical producers. In the Conclusion, Steen summarizes these changes:

The “American” synthetic organic chemicals industry gained its identity by transforming the niche markets of German dyes and pharmaceuticals into mass-produced commodity chemicals, developing the aliphatic branch of chemistry and drawing on the expertise of chemical engineering (p 292).

Implicitly and/or explicitly, a number of very important themes of the historiography of American and international science and industry of the period 1880–1930 are addressed in this book. The most significant is that denominated by my opening scenario: how did American science-based industries move from backwardness and dependency (particularly on Germany) to front-runner positions, independence, and high international competitiveness? Secondly, what role(s) did war, in this era, World War I, play in these developments? Thirdly, what factors in American politics and culture of this period were significant? And finally—this one already mentioned—what changes of industrial organization and outlook (“industrial culture,” if you will), were at play in these transformations?

These themes are the ones that dominate the bulk of the book. The opening chapter focuses on German and American synthetic organic chemicals industries; the German industries “dominated the world’s production of synthetic organic dyes between 1870 and 1914” (p 23) as well as pharmaceuticals, whereas the contemporaneous American dyes and pharmaceutical industry was “almost negligible” (p 33) but with potential from the inorganic chemicals industry. Chapters two through seven trace out the war-time and post-war industrial and government actions to develop and maintain this industry. Chapter eight focuses on the theme of changes in industrial organization and outlook for five major synthetic organic chemical manufacturers.

Of particular importance is the backdrop of World War I. In chapter two, Steen traces the evolution of the synthetic organic chemicals industry in a number of companies during the war, at the end of which Steen assesses the industry as “precariously built on unsure foundations” (p 76). However, the war itself provided important stimuli and resources for future potential development: expertise in utilizing organic chemicals in high explosives, augmentation of raw materials, and experience in large-scale production, for example. The war also engendered strong nationalistic and anti-German sentiments throughout American society, including the community of chemists,

and this helped to foster the impulse to develop “German” synthetic organic chemicals. A dramatic example of this sentiment and its implication was the rhetoric of the chemist, Charles Holmes Herty (President of the American Chemical Society in 1915 and 1916), who wrote of German “enslaving power” over the nascent American industry (p 126). Universities also reoriented towards advanced training in organic chemistry despite shortages in students and laboratory materiel (previously obtained from Germany), and formed consulting liaisons with industry.

But it was the federal government’s support of the nascent and instable synthetic organics industry that made a critical difference. Before the US entry into the war in 1917, the government took steps to aid the industry largely through market information supplied by the Department of Commerce. Although the Democratic administration was ideologically against protection through high tariffs (and the textile industry was not in favor), lobbying by chemists such as Herty and the chemical industry did result in a tariff bill being enacted in 1916 although one not completely satisfactory to the industry. Once the US entered the war, far more draconian measures against the German industry and its property and patents in the US were enacted, such as the “Trading with the Enemy Act” of October 1917, with its attendant Office of Alien Property and Alien Property Custodian. A. Mitchell Palmer, the Alien Property Custodian and Francis P. Garvan, head of the Office’s Bureau of Investigation, steered the Office of Alien Property towards confiscation and sale of the property and sequestering of the patents of the German synthetic organic chemicals industry. These latter were deposited in and administered by a “Chemical Foundation,” founded by the Alien Property Custodian in 1919, with Garvan as its first head. More generally, a protracted “economic war” was waged against German industry for the four years after the armistice augmented by industrial self-interest and reflective of the persistence in the United States of anti-German sentiment and intense isolationism. This climaxed in the Fordney-McCumber Tariff Act of 1922, placing “the steepest tariffs ever on [imported] dyes and intermediates derived from coal tar” (p 199). Throughout the rest of the decade, the US synthetic organics industry continued to benefit from governmental support and judicial decisions against German patent compensation claims.

If this were a literary work—a play or a novel—this narrative might build up to the satisfying dénouement that the US had come up to parity with Germany in the manufacture of the traditional dyes and pharmaceuticals

by the book's terminal date, 1930. But history is not literary narrative and, as was mentioned near the start of this review, the American synthetic organic chemicals industry in fact veered off in a different direction towards aliphatic rather than aromatic organic chemicals during the 1920s.

How this came about—and, indeed, how the major US chemical manufacturers were transformed—in this decade is the subject of the eighth and final chapter, aptly titled “An ‘American’ Industry, 1919–1930.” After detailing mergers and changes in I.G. Farben in Germany (e.g. high pressure organic synthesis under the leadership of Carl Bosch) and the recapturing of a portion of the American market for dyes, Steen turns to analyzing changes in the major US synthetic organic chemicals producers: National Aniline & Chemical Company/Allied Dye & Chemical Corporation, E. I. du Pont de Nemours & Company, Dow Chemical Company, Union Carbide and Chemical Company, and Bakelite Corporation.

In fact, there is something of a literary “moral fable” contained in this chapter: The first of the companies, National Aniline & Chemical Company, was “the largest American manufacturer of chemical dyes” at the end of the war (p 250) and its merger with other firms to form the Allied Dye & Chemical Corporation in 1921 resulted in a chemical concern that was second only to Du Pont. But National Aniline, which continued to specialize in synthetic dyes, fell on hard times due both to insufficient technical ability and decisions at the top by Orlando F. Weber, former president of National Aniline who became president of the merger company, to downplay synthetic dyes in favor of nitrogen-based products perhaps because he came to realize that “the profitability of dyes, which depended heavily on the tariff, was too uncertain in the face of steep international and domestic competition” (p 254).

In contrast, the other companies discussed in this chapter all focused or came to focus on aliphatic chemical products. Moreover, they all participated in the changes that produced the industrial physiognomy of Steen's “new ‘American’ industry” as detailed earlier in this

review. Her account of Du Pont is the most elaborate and depends in part on the magisterial study of Du Pont by David Hounshell and John Kenly Smith.

The American Synthetic Chemicals Industry: War and Politics, 1910–1930 is an important book. Its narratives and arguments are rich and intricate. With such an accomplishment before me, I hate to ask for more from the author but this is, after all, the function of a reviewer's critique. One addition that would have enriched Steen's narrative is more background context on the general economic ups and downs of the period, particularly the post-World War I period (domestic and international). As I was organizing my thoughts, I came upon a review of a book on the depression of 1921 (1). I can hardly expect Steen to refer to this book, which was just published, but she does in fact make passing reference to this episode several times. It would have been valuable to have some sustained background narrative about economic change.

My second “wish” is for more industrial context for Steen's critical eighth chapter on the development and change-of-direction of the synthetic organic chemicals industry in the 1920s. The obvious context here is the mutually reinforcing developments of petrochemical and automobile industries. In her Conclusion, Steen raises a counterfactual argument about what might have transpired with the synthetic organic chemical industry had World War I not occurred. One could raise the same kind of counterfactual regarding these contextual industries: how might/might not the American synthetic organic chemicals industry have been sustained and developed in the 1920s had these industries not been developing so vigorously? But these are desires engendered by the stimulus of a rich and highly informative book.

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References and Notes

1. J. Grant, *The Forgotten Depression: 1921: The Crash That Cured Itself*, Simon & Schuster, NY, 2014. Reviewed in *The Economist*, Nov. 8–14, 2014, pp 84–85.

Up from Generality: How Inorganic Chemistry Finally Became a Respectable Field, Jay A. Labinger, Springer, Heidelberg and New York, 2013, ix + 77 pp, ISBN 978-3-642-40119-0, \$54.99, softcover (ISBN 978-3-642-40120-6, \$39.99, eBook).

Science wars constitute an everyday occupation of scientists. Indeed, science is carried out by heterogeneous communities of research and education in competition for limited quantities of economic, political and symbolic capital. Each scientific community tries to rake in as much funding, power, and recognition as its members think they deserve according to their advancement of knowledge and their development of applications. A structural feature of science and an inner factor of dynamism, science wars drive the history of science and technology. This is the underlying idea used by Jay A. Labinger in his latest book about the history of inorganic chemistry in the United States from the nineteenth century onwards. The main thesis of *Up from Generality: How Inorganic Chemistry Finally Became a Respectable Field* is that the development of inorganic chemistry in US Academia can be read as a gradual process that turned a fuzzy, backward sub-field of chemistry in the late nineteenth century into “an independent, intellectually viable discipline” (p ix) during the second part of the twentieth century, at equality with “the other main branches of chemistry,” organic and physical chemistry.

The explicit goal of this short historical monograph of seventy pages or so is to demonstrate how and why inorganic chemistry passed from minor to major status among chemical sub-fields during the twentieth century. In spite of a broad title, the scope of the book focuses on American Academia during the twentieth century. The demonstration consists of an introduction, four chapters, and a conclusion. For each chapter, the current review describes the historical content and analyzes the argumentation and methods. The introduction is a seven-page chapter that mixes personal reminiscences, other testimonies, and selected citations from historical textbooks. It stresses the discrepancy from which the book originated: an increasing prestige of inorganic chemistry experienced by the author himself when he was a young inorganic chemist in the 1960s in US Academia; a weak status and a negative definition—what is not organic—in the nineteenth century and still in the late 1960s at Harvard, the field being “more or less conflated with general chemistry” (p 2). The entire demonstration thus relies on a regressive logic from the present to the past. The major risk of such a perspective is to replace a complex historical process made of contradictions,

incoherencies, and alternatives, by an over-simplified one-way road to the present.

The core of the book consists of four well-balanced chapters of a dozen pages each with several archival pictures of scholars and a bibliography at the end of each chapter. Chapter 2 gives a short historical account of inorganic chemistry in the nineteenth century thanks to several top-rank textbooks on the history of chemistry. The synthesis is interesting even though it magnifies the heroes of chemistry like Dmitri Mendeleev for the periodic table of elements and Alfred Werner for his theoretical contribution to coordination chemistry. One can regret that the selected quotations of the two first chapters are systematically used to stress one single idea—the sociological weakness of inorganic chemistry in the science wars against organic and physical chemistry—whereas neither explicit definition nor list of sub-fields is given to explain what was the inorganic chemistry of the time. The author usually takes for granted the (implicit) features of the inorganic chemistry he has known during his career. Instead, a temporal analysis in the changing definitions, sub-fields, practices, institutions, identities, etc., would have been much more convincing to explicate the *historicity* of inorganic chemistry from the nineteenth century onwards. Thus, the discipline is *naturalized* through expressions such as “birth,” “renaissance,” and “premature,” as if there was an essence of inorganic chemistry.

Chapter 3 describes the building of inorganic chemistry in US Academia during the twentieth century and stresses “a major transition in [its] status” in the 1950s and 1960s (p 17). It convincingly crosses a set of anecdotes told by some American and British inorganic chemists and a thorough quantitative study. This study, whose method is detailed in an appendix (pp 73-75), relies on statistical correlations to demonstrate that the institutional representation of inorganic chemists (for example, the number of rewards) reveals the symbolic status of inorganic chemistry (for example, respectability). It focuses on two central institutions in US Academia: for science in general, the National Academy of Sciences; for chemistry in particular, the American Chemical Society, including the *Journal of the American Chemical Society*. A good quantitative analysis would have required a qualitative discussion about the choice of variables and the meaning of results. Why, for example, does the method favor published articles and institutional rewards rather than university chairs? Why is there no mention of industrial applications, patents, or companies?

From the national level of chapter 3, chapter 4 dives into the local dimension of one laboratory of Caltech. The

goal is to stress the importance of personal factors—the rivalry between Donald Yost and Linus Pauling—to explain scientific dynamics and inertia. This detour allows the first exhibition in the book of archival documents (apart from pictures): a list of faculty chemists drawn by Pauling in 1944 in which Yost did not appear (p 37). A first definition of inorganic chemistry extracted from a 1930 Caltech curriculum is also given here, which is very late. This chapter could have given the opportunity to discuss the different available sources and to organize them into hierarchy since a 1930 curriculum of Caltech, a 1944 memo by Pauling, a 1956 conference from Ronald Nyholm, and a 2002 testimony of Fred Basolo do not have the same status as sources of information.

Chapter 5 shifts from description to explanation. It tries to justify why inorganic chemistry gained social “respectability” from the 1950s onwards. This is the most questionable chapter of the book because historical clues are replaced by inner conviction. The author mentions “external” factors (quantum theory and experimentation) that may have played a role but he prefers to pray for his own chapel: “I find it hard to accept that the major impetus came from outside the field [...]: inorganic chemists themselves were the movers and shakers” (p 51). The main “agents [...that] made inorganic chemistry truly respectable” were the domains of “asymmetric catalysis” and “organometallic chemistry” through the comprehension of reaction mechanisms. This is a strong claim but there is no historical evidence to support this: four reaction mechanisms are given with current notations and without publication reference (pp 53-55). There is a confusion between history and memory here. Indeed, the *curriculum vitae* of the author reads: the “chemistry research [of the author] has been focused in the areas of organotransition metal chemistry and energy-related catalysis. Many of his contributions have taken the form of mechanistic explanation” from the late 1960s onwards (p 77). The author is so linked to the milieu from which he seeks to write the history that he deeply relies on personal feelings and memories. To this respect, the academic lineages (p 60) are interesting to question since they are both historical tools to understand intellectual and institutional genealogies and family trees to identify the self and the others (the author belonging to the lineage of John Osborn).

The conclusion (chapter 6) shifts from history/memory to the sociology of scientific disciplines. It aims to account for the formation of inorganic chemistry through the four-item model of S. Frickel and N. Gross to define “scientific/intellectual movements:” avail-

ability of resources, dissatisfaction, mobilization, and identification of people. At the end of the conclusion, the different sub-fields of inorganic chemistry are eventually listed. Besides the already mentioned coordination and organometallic chemistry, the author adds bioinorganic and solid state chemistry (linked to materials science), which developed from the 1960s onwards (p 66). So why ignore them in chapter 5 (and more generally all over the book) to account for the rise of inorganic chemistry? It is also a pity that the identification of inner factors prevents the consideration of broader evolutions of the twentieth century, including instrumental revolutions, cold war, industrial developments, and the policy-making of technoscience.

To conclude this review, how can *Up from Generality: How Inorganic Chemistry Finally Became a Respectable Field* be read and understood? Certainly, the book is good reading, contains plenty of original anecdotes, citations, and memories from English-speaking inorganic chemists, and introduces a heuristic quantitative approach. Its scope is certainly narrower than expected: the book is a contribution to the history of coordination chemistry, a sub-field to which the author belongs. To write a history of inorganic chemistry would have required taking into account several other sub-fields such as high temperature materials, solid state chemistry, gas chemistry, etc. It is interesting and valuable that scientists contribute to the history of their own science since they know the culture from inside. This may, however, lead to a discourse of legitimation of the self (with regards to others) and of the present (with regards to the density of the past). In another context, the historian of mathematics Ivor Grattan-Guinness called this attitude the “royal road to me.” Labinger’s book presents the *royal road* to (current) inorganic chemistry as a gain of “respectability” by the “generalization” of theoretical frameworks. The narrative is a systematic trial to show that all the elements of the science wars converge towards the restoration of the injustice (from backward to forward status) and the advancement of the rationality (from singularity to generality). In the meantime, it lacks the complex interactions between human beings and natural things that drive the history of science and technology. When epistemic, technical, economical, political, social, and cultural factors are in interaction, justice and rationality become nothing but two small pieces of the historical puzzle.

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COMMENT AND RESPONSE

Review of *Organic Chemistry Principles in Context: A Story Telling Historical Approach*

The last issue of the *Bulletin* included a review of *Organic Chemistry Principles in Context: A Story Telling Historical Approach*. The book is unusual among those routinely reviewed in this journal because it is not primarily a work of history but a textbook of organic chemistry or a supplement to such a textbook. In its own field the book is also noteworthy in its pedagogical approach—not least in its abundance of historical content, which is what makes it relevant to readers of the *Bulletin*.

The following pages contain, at my invitation, a comment on the review from the book's author, Mark M. Green, and a response by the reviewer, Peter J. Ramberg.

—Editor

Comment by Prof. Green

Dear Editor,

There are several corrections necessary in the review of *Organic Chemistry Principles in Context: A Story Telling Historical Approach*, concerning the historical material, which follows below. The review appeared on page 99 of the latest issue of the *Bulletin for the History of Chemistry*, volume 39, number 1. I've reproduced the contested remarks in the review in the order they appeared. Each is followed by the proposed corrections taken from the quoted historical texts and also, when appropriate, notes to the editor concerning the particular points made.

In a second section of this note, I have made further comments, following this section, about, what I consider to be unjustified more general criticisms of the book by the reviewer. Thank you for the opportunity of responding to the review in this manner.

Historical Accuracy

From the review:

There are also some errors in the history. It repeats, for example, the myth that Friedrich Wöhler sounded the "death knell" for vitalism when he made urea in 1828...

In *A History of Chemistry* volume IV by J. R. Partington is found a description of Wöhler's work on the synthesis of urea (1):

Dumas (1830) said: "all chemists have applauded Wöhler's brilliant discovery of the artificial production of urea, ..." ... Liebig (1831) regarded the discovery of Wöhler and the work of Berzelius on racemic acid as "the first beginning of a truly scientific organic chemistry". Liebig (1843) spoke of urea as "composed in a so-called artificial way almost immediately from its elements", and thus "the natural barrier (die natürliche Scheidewand)

which until then separated the organic from the inorganic compounds had fallen, and a classification of chemical compounds into organic and inorganic in the earlier sense had no natural basis". Of later writers, Hofmann (1888) spoke of "the synthesis of urea" as "an epoch-making discovery" and it was so regarded by others (1900 and onward).

I am aware that there is controversy about the loss of belief in vitalism over the 19th century. Does the reviewer suggest that Wöhler's work was not a critical input into this process? What Partington wrote is certainly evidence that it was a critical input, a death knell, (allowing use of metaphor), perhaps not heard by all immediately.

From the review:

....Archibald Couper was "scooped" by August Kekulé about the tetravalence of carbon and the self-linking of carbon atoms (page 33), because Adolphe Wurtz kept Couper from publishing his paper for a year until 1858, three months after Kekulé's paper, by which time Kekulé had "gained all the credit for the tetravalence of carbon." It's unclear where Green found this story, as it is not in the standard historical literature.

In *Image and Reality*, by A. J. Rocke, appears the following (2):

His (Couper) new chemical theory announced both the tetravalence and self-linking of carbon atoms, the second statement appearing, as he thought, for the first time. Unfortunately, Kekulé's "theory of aromaticity of the elements" paper defending the same proposal had already appeared in print, in May 1858. The most unhappy aspect of the matter is that earlier that spring (probably in March or April) Couper asked Wurtz to present this paper to the Académie, but Wurtz was not yet a member of the Académie and so had to request the favor of a colleague. Eventually it was Dumas who presented Couper's paper, but too late to procure priority for the thesis of carbon self-linking. Couper was distraught at the disappointment, and he angrily confronted Wurtz. Wurtz then asked him to leave the laboratory.

From the review

Green also claims that Kekulé published his benzene theory in 1865, "sponsored by Wurtz," (page 169) when in 1865, Kekulé had been a professor in Ghent since 1858 and had left Wurtz's laboratory long ago in 1852.

In *Image and Reality*, in the section on Aromatic Apparitions, appears the following (3):

Considering the events that immediately followed Kekulé's trip to Paris, it seems reasonable to believe that he went there specifically to talk to his good friend Adolphe Wurtz about his new theory.

A few days later, Wurtz presented Kekulé's benzene theory to the Société Chimique in Paris.²⁹ (Kekulé, *Substances aromatiques* (1865)) Kekulé began by pointing out that no one, "as far as I am aware," had attempted to apply the theory of atomicity of the elements to aromatic compounds. He stated that he had had a "fully formed idea" on this question since 1858, having published hints in that direction in his major paper of that year, but he had not regarded it as appropriate to unveil it publicly and in detail until now.

In the reviewed text the following appears on page 169: ".....he wrote his now famous paper in French, because he was a professor in Belgium." Criticism of the book by the reviewer by noting that Kekulé was a professor in Ghent (Belgium) is surprising considering that the book took note of his position in Belgium. In addition to the unjustified criticism concerning Kekulé's position in Belgium, noting Rocke's quoted material above, "sponsored by Wurtz" is certainly justified.

From the review:

Linus Pauling did not win his Nobel Prize for proposing the structure of the alpha helix (p 10), but for his work on the nature of the chemical bond during the 1930s, a fact that is easily checked on the internet.

On the Nobel Prize web site is found the following statement (4):

The Nobel Prize in Chemistry 1954 was awarded to Linus Pauling "for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances".

In the presentation speech is found:

On this basis Pauling deduced some possible structures of the fundamental units in proteins, and the problem was then to examine whether these could explain the X-ray data obtained. It has thus become apparent that one of these structures, the so-called alpha-helix, probably exists in several proteins.

The alpha-helix, deduced by Pauling from his effort on the chemical bond, was certainly a very important part of the body of work for which Pauling won the Nobel Prize as seen from the web site quoted above although I agree with the criticism that I should have stated more clearly the central role of the chemical bond. There is an

extensive discussion on page 9 of the book of Pauling's role (and his picture) in development of understanding of the chemical bond.

These sentences are in the review: "These fundamental errors are reason enough to suspect others throughout the book." "The strength of Green's approach is therefore not in his use of history, but in his extensive use of specific real-world problems in organic chemistry,"

These so-called historical errors are especially unfair in the review, considering that the reviewer himself may be reasonably questioned about his own historical accuracy. There is no basis to make a global condemnation of the historical aspects of the book.

General Criticism

The following sentence appears in the review:

The general assumption throughout the text is that the first publication of theories resembling our own are unproblematic and were immediately accepted by chemists as correct.

Only reading the reviewed text can convince one that this statement in the review is entirely unjustified, but for just a few of many examples one turns to the discussion in the book of Kekulé's proposal for the structure of benzene. Section 6.6 discusses the objections to this theory and the manner in which these objections were overcome. The section heading is: "Objections to Kekulé's hexagonal ring structure for benzene required an explanation that was the equivalent to the concept of resonance." (p 173)

Here is another example, section 3.3 (p 74) with the heading

It took many years for chemical science to accept the idea that rings did not have to be flat and further that acceptance of this idea could explain many aspects of the chemical behavior of cyclic molecules. An important advance, as is the situation in science, was the use of a new kind of instrument applied to the problem.

Here is another example. Section 4.3 on page 107 with the section heading

It took a great deal of time before chemists accepted the possibility that the carbon skeleton of a molecule could change, and then even longer to realize that the agent of change was a chemical intermediate with a positively charged carbon, a carbocation.

Here is another example. Section 8.8 on page 267 with the section heading: "Stereochemistry: Why Krebs' proposal was thought to be impossible."

The criticism in the review is really quite astonishing considering anyone who has read the book. The examples above are just exemplary of the way the book is written with regard to how theories were dealt with.

The criticism in the review of the beginning of Chapter 1 about showing the line structures of cellulose and starch without an introductory explanation does not take account of the approach of the book, which, as pointed out in the Introduction, is presented as a top-down approach or as some say, backwards learning. These structures, drawn in the manner used by organic chemists, which are incomprehensible to the student at this stage in their learning, as intended by the author, form the basis of the student using the structures to learn about the meaning of these lines and as well the missing carbon and hydrogen atoms to make up the formula of glucose. This explanatory material occurs in the following pages. The rest of the book follows this philosophy. The book is not only about context with a historical background but also about pulling the principles of the science out of complex phenomena arising from application of these principles. This approach is one of the original aspects of the book, which is not only concerned with context and history but also with top-down learning in which the principles of the science are discovered by the student in the complex phenomena arising by application of these principles.

The sentence in the review "but what is there is little more than expanded versions of the side boxes found in other texts that are largely unconnected to the chemistry itself," is hard to understand if one looks at large numbers of organic chemistry textbooks with boxed in historical information. There is so much more in this book, in which the historical aspects are interwoven with the text, than any other beginning organic chemistry text in use today. Reading *Organic Chemistry Principles in Context: A Story Telling Historical Approach*, will demonstrate the truth of the claim.

Finally, there are the critical remarks in the review about use of the book and the necessity of other sources of information. It is amazing to make a criticism out of this fact without acknowledging that that book proposes such a use. Is the reviewer suggesting that such a use is not a good idea? Apparently not from what is written in the review. On page x in the introductory part of the book there is the suggestion that the book might serve well as

a supplementary text together with a more conventional textbook. This possibility is the primary reason why the price is so low (\$25 for paper and \$10 for e-book) to exactly allow such a possibility, which can bring history and context to the study of organic chemistry. To make a criticism out of something the book itself proposes as a use, without acknowledging what is in the book on that precise point, as if that were a problem, is especially unjustified. The low price and the suggestion for use as a supplement to enhance appreciation of historical aspects of the science could have been a point of praise.

Mark M. Green, Professor of Chemistry, New York University Polytechnic School of Engineering, mgreen@nyu.edu

References and Notes

1. J. R. Partington, *A History of Chemistry*, Macmillan, London, 1964, pp 259-60.
2. A. J. Rocke, *Image and Reality: Kekulé, Kopp, and the Scientific Imagination*, University of Chicago Press, Chicago, 2010, p 121.
3. Ref. 2, p 199.
4. Nobel Foundation, http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1954/

Response by Prof. Ramberg

Dear Editor,

The purpose of a book review is to tell potential readers of the book about its contents, the author's purpose, and to discuss the strengths and weaknesses of the book as written. As I was reading Prof. Green's book, I had truly mixed feelings about it. I admired very much the approach and the examples, as well as how Green completely reorganized the approach to organic chemistry. But my admiration was tempered by what I perceived as shortcomings, that in an all too brief review I could not present fully. I am glad to explain myself here in greater detail, allowing readers to decide if my review was accurate.

Wöhler and Vitalism

Green cites a passage from volume 4 of Partington's *History of Chemistry* (1) in support of his claim that Wöhler sounded the "death knell" for the vital force. But consider that the citations in the passage refer exclusively to the artificial nature of Wöhler's synthesis, which was cause for excitement among chemists at the time. Nothing in this passage actually refers to the fate of the vital force! Importantly, the pages from Partington cited by Green are in a section labelled "isomerism," and Partington himself does not discuss vitalism at all in this section of the book. Looking at "vital force" in the index,

furthermore, shows only three relevant entries, one of which refers to Jakob Berzelius' concept of the vital force developed in his 1827 textbook that remained unaltered until his death, and another on Justus Liebig's concept of vital force developed in the 1840s. Partington's history cannot therefore support the claim about Wöhler's synthesis and vitalism, because he does not discuss the effect of Wöhler's synthesis on the vital force.

In the fifty years since Partington's encyclopedic oeuvre, historians have shown clearly that Wöhler's synthesis could not have been the demise of vitalism, because "vitalism" was not a single, comprehensive theory, but a variety of different theories about *biological systems*, and vitalistic theories continued to appear long after Wöhler's synthesis, as the examples of Berzelius and Liebig show. The idea that organic *compounds* possessed a mysterious vital force began to disappear at least as early as 1814, when Berzelius showed that organic compounds followed laws of constant chemical composition, albeit following different rules than inorganic compounds. By the 1820s, the principal stumbling block for the synthesis of organic compounds was not ignorance of a different kind of chemical force that held organic compounds together, but the greater complexity of the composition of atoms in organic compounds. For a more detailed look at the current understanding of Wöhler's urea synthesis, I would refer readers to John Brooke's 1968 article, Chapter 10

of Alan Rocke's *Quiet Revolution* (1993), and my own articles on the meaning of the urea synthesis (2).

Linus Pauling and the Nobel Prize

Green notes correctly that the Nobel Prize citation about Pauling refers to both his work on the nature of the chemical bond and his successful application of that theory to various complex molecules. It is possible that the elucidation of the α -helix was the tipping point that resulted in finally awarding Pauling the 1954 Nobel Prize in chemistry, and I would not disagree with that claim. But I do disagree with what Green actually writes about Pauling's work and the Nobel Prize on pages 9 and 10. On page 9, Green describes the theoretical problem of tetrahedral bonding in the carbon atom that Pauling solved in the 1930s with the concept of hybridization. Green then writes that Pauling received two Nobel Prizes, one in 1954 and 1962, "neither of which was for his solution" to this problem. Green then mentions Pauling's equally important work on electronegativity, and then, finally (page 10), "And we still are not mentioning Pauling's contribution that won him his first Nobel Prize, for proposing a structural element of proteins, the α -helix." Given this narrative, what is an unknowing reader to conclude about the reason for Pauling's Nobel Prize? Pauling's prize was for lifetime accomplishment, including the α -helix, but not exclusively because of it, as Green explicitly argues in the text. After all, Pauling's general work on the chemical bond (which included hybridization, resonance and electronegativity) is noted first in the Nobel Prize citation.

Kekulé, Couper and Wurtz

In his book, Green recounts a story that Adolphe Wurtz "delayed" Archibald Couper's paper on the self-linking of carbon atoms, allowing Kekulé to publish the idea first and therefore get full credit. Green's book asserts (page 33) that Couper had prepared his paper on the self-linking of carbon atoms in 1857, and that Wurtz "delayed" its publication until 1858. On page 169, Green writes more forcefully that Wurtz "had blocked Couper's paper from appearing so that Kekulé received all the credit." This is, unfortunately, not how Alan Rocke's *Image and Reality* has described the event (3). According to Rocke, Couper had prepared his paper for publication in the spring of 1858, and, as Rocke recounts *in the very passage quoted above by Green*, Wurtz could not present it to the academy because he was not a member, and the reading of the paper was delayed until Jean-Baptiste

Dumas could present it later in the spring. In other words, according to Rocke's account, Wurtz did not actively "block" or "delay" Couper's paper as Green explicitly claims in his text.

Consider also Rocke's analysis of Couper's full paper (3), an analysis which needs to be considered closely together with the historical fact that Kekulé's paper appeared in print before Couper's. Rocke argues clearly that Couper's paper was likely read with very skeptical eyes, and only looks "correct" with hindsight. Chemists *at the time* found Couper's ideas and formulas too speculative and not sufficiently grounded in empirical evidence, no matter how modern they appear to us. This reluctance to accept Couper's paper in part led to giving Kekulé priority.

I should also note here that assigning Kekulé full credit because he published first is also somewhat problematic, because Kekulé himself was somewhat unclear on how to apply his principles and reluctant to present formulas graphically. In 1861, Aleksandr Butlerov argued more forcefully for the consistent application of Kekulé's principles to connect all atoms in the molecule to form a "chemical structure," a term that Butlerov coined. The message to students reading about this episode should be that similar ideas often appear simultaneously in different forms. Ideas and theories in chemistry that we take for granted today do not simply appear fully formed: they are shaped by multiple chemists within a specific historical context full of contingencies (like the factors that delayed publication of Couper's paper).

Green's comments on Kekulé's first publication on the structure of benzene are less problematic, particularly in light of his clarifying the manner in which Wurtz "sponsored" the publication. Still, Green's book says (page 169) that Kekulé's 1865 paper was "again sponsored by Wurtz," naturally leading the reader to assume that Wurtz sponsored Kekulé's work in 1858, which he did not.

I am glad that Green consulted Rocke's book in writing his own, but it is important to summarize accurately what Rocke (and Partington) has written. These examples of misreading or misinterpreting the historical literature are what prompted me to write in the original review that I *suspected* other *possible* historical errors in the book. I did not make a "global condemnation of the historical aspects of the book." I was informing readers that there *may* be misrepresentations of the historical literature, and that they should examine the book with that in mind. This is especially important, as Green does not, except in a few places, indicate his sources for the claims he makes.

Acceptance of Theories

Green cites several passages from his book to show that he understands that chemists did not immediately accept theories. The first passage, a caption from page 173, notes that "Objections to Kekulé's hexagonal ring structure for benzene required an explanation that was the equivalent to the concept of resonance." On page 173, Green describes, correctly, the problem with Kekulé's benzene formula, but then he describes Kekulé's solution to this problem as a proto-resonance formula, and then jumps to Linus Pauling's description of benzene in the 1930s, skipping seventy years of intense discussion by chemists about benzene's structure that did *not* involve resonance (4). The second example, involving the elucidation of the chair forms of cyclohexane, is less problematic, although the passage Green quotes raises the issue about why chemists thought of rings as flat for so long.

Pedagogical Issues

In my review, I noted that the book would come with a steep learning curve. I understand Green's pedagogical approach and described it in the review. My view is not that his approach is *wrong*, as he implies in his letter, but that it is different, and that not all students will benefit from it (5). Green's approach is admirable. I have myself thought about how to incorporate historical material into my organic chemistry lectures that would explain the epistemological foundations of organic chemistry.

Green is correct that there is certainly much more material in his book than in typical textbooks on the chemists who developed organic chemistry. My argument is not with the quantity of the material, but its relevance. For example, as noted by another reviewer, what lessons are students to learn from the story about R. B. Woodward's lack of sleep, his loathing of exercise, or his chain smoking during his marathon lectures (6)? It is useful, as I noted in the review, to present the material as a set of problems that chemists have solved. But how should students use the historical information Green presents to understand organic chemistry? What lessons should they learn about chemistry as a science? In his introduction (page xi), Green himself tells students not to worry about reproducing the historical material. If this is the case, then why is it there? Unless Green integrates this material fully into the chemistry and gives students a clear idea why each historical episode is important for understanding the nature of chemistry, the historical material serves as a distraction or a diversion.

Regarding Green's final point, we agree that his book could be used as a supplement to a traditional text. In neglecting to mention in my review that the author envisioned such a use, I did not intend to suggest that such a use of the book was a bad idea. But I did mean to express doubt, based on my own experience of twenty years of teaching organic chemistry, that the text would work as a stand-alone textbook. Two instructors from my department came to the same conclusion after looking through the book. Nevertheless, I would encourage readers and instructors to decide for themselves whether and how to use this book in the classroom.

Peter J. Ramberg, Truman State University, ramberg@truman.edu

References and Notes

1. J. R. Partington, *A History of Chemistry*, Macmillan, London, 1964, pp 259-60.
2. A. J. Rocke, *The Quiet Revolution: Hermann Kolbe and the Science of Organic Chemistry*, University of California Press, Berkeley, 1993. J. H. Brooke, "Wöhler's Urea, and its Vital Force: A Verdict from the Chemists," *Ambix*, **1968**, *15*, 84-114. P. J. Ramberg, "Myth #7: That Friedrich Wöhler's Synthesis of Urea in 1828 Destroyed Vitalism and Gave Rise to Organic Chemistry," in K. Kompourakis and R. L. Numbers, Eds., *Historical Myths about Science*, Harvard University Press, Cambridge, MA, 2015 (forthcoming). P. J. Ramberg, "The Death of Vitalism and the Birth of Organic Chemistry: Wöhler's Urea Synthesis in Textbooks of Organic Chemistry," *Ambix*, **2000**, *47*, 170-195.
3. A. J. Rocke, *Image and Reality: Kekulé, Kopp, and the Scientific Imagination*, University of Chicago Press, Chicago, 2010, p 121.
4. See for example, chapter XII in C. A. Russell, *The History of Valency*, Humanities Press, New York, 1971, and S. G. Brush, "Dynamics of Theory Change in Chemistry: Part I. The Benzene Problem, 1865-1845," *Studies in History and Philosophy of Science*, **1999**, *30*, 21-79.
5. My review was not the only one to question Green's pedagogical approach. See H. Hopf, "Organic Chemistry Principles in Context. A Story Telling Historical Approach." By Mark M. Green," *Angew. Chem. Int. Ed. Engl.*, **2013**, *52*, 1365-1366.
6. S. R. Pruett, "Review of *Organic Chemistry Principles in Context: A Story-Telling Approach*," *J. Chem. Educ.* **2014**, *91*, 624-625.

ERRATA

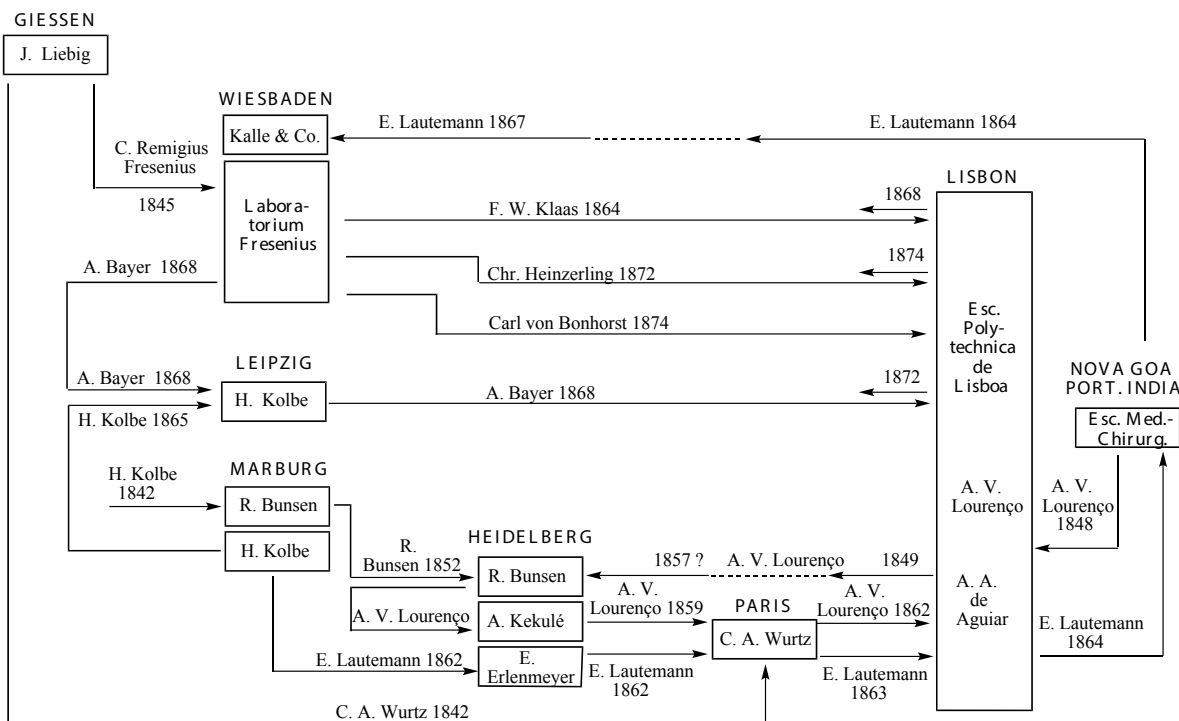
A number of errors crept into the article “A Transnational Network of Chemical Knowledge: the *Preparadores* at the Lisbon Polytechnic School in the 1860s and 1870s” by Bernardo Jerosch Herold and Wolfram Bayer (*Bull. Hist. Chem.*, 2014, 39(1), 26-42). The errors are entirely the fault of the editor, specifically of working from an earlier version of the manuscript than the final version. The errors are listed below. The version on the *Bulletin* website for issue 39(1) is a corrected version. We regret the errors.
—Editor

- p 26, author affiliations: Change Bernardo Herold’s email address to herold@tecnico.ulisboa.pt. Change Wolfram Bayer’s affiliation and address to Institut für

Corpuslinguistik und Texttechnologie, Österreichische Akademie der Wissenschaften, Sonnenfelsgasse 19/8, A-1010 Vienna, Austria

- p 26: Change sentence 2 of paragraph 2 to: The influence of his older colleague Agostinho Vicente Lourenço (1822-1893), an élève of Adolphe Wurtz (1817-1884), is not alone sufficient to explain the success of Aguiar’s research oeuvre. As it happens, some papers are co-authored with chemists with German surnames, who spent some time in Lisbon.

- p 29, column 1, line 18: Change July 1863 to spring 1863.



- p 29, col. 2, line 19: Change June 1863 to spring 1863.
- p 33, col. 2, beginning at line 30: Replace the sentence that starts, “The keywords Bayer ...” with The keywords Bayer and Bielitz in Google, however, did not yield any information on Alexander Bayer but did instead on the famous inventor of the Bayer process for the extraction of aluminum oxide from bauxite—Karl Joseph Bayer, born in 1847 (51) apparently coincidentally in the same place.
- p 34, col. 1, line 17: Change passed away to died.
- p 34, paragraph 1 of section Publications of Alexander Bayer: Delete the first sentence. Change the second sentence to “In the present publication we will concentrate on Bayer’s work done in Leipzig and Lisbon, i.e., between 1868 and 1871.”
- p 35, col. 2, line 27: Change passed away to died.
- p 36, col. 1, line 4: Change 55 to 52.
- p 37: Replace Figure 2 with the accompanying corrected figure.
- p 42, final paragraph: In first paragraph change translator to translator and philologist. Change sentence 3 to: He has several publications on Austrian literature and a number of scientific and literary translations from French to German. Change sentence 4 to: Working, at present, on digital humanities projects with the Austrian Academy of Sciences, he recently took an interest in the life of his great granduncle Karl J. Bayer, the inventor of the Bayer process for the preparation of alumina from bauxite.

Pacificchem 2015

The 2015 International Chemical Congress of Pacific Basin Societies (Pacificchem), will take place in Honolulu, Hawaii, USA, December 15-20, 2015. The conference is sponsored jointly by the American Chemical Society (ACS), the Canadian Society for Chemistry (CSC), the Chemical Society of Japan (CSJ), the New Zealand Institute of Chemistry (NZIC), the Royal Australian Chemical Institute (RACI), the Korean Chemical Society (KCS), and the Chinese Chemical Society (CCS). The American Chemical Society is the host society for the 2015 Congress.

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