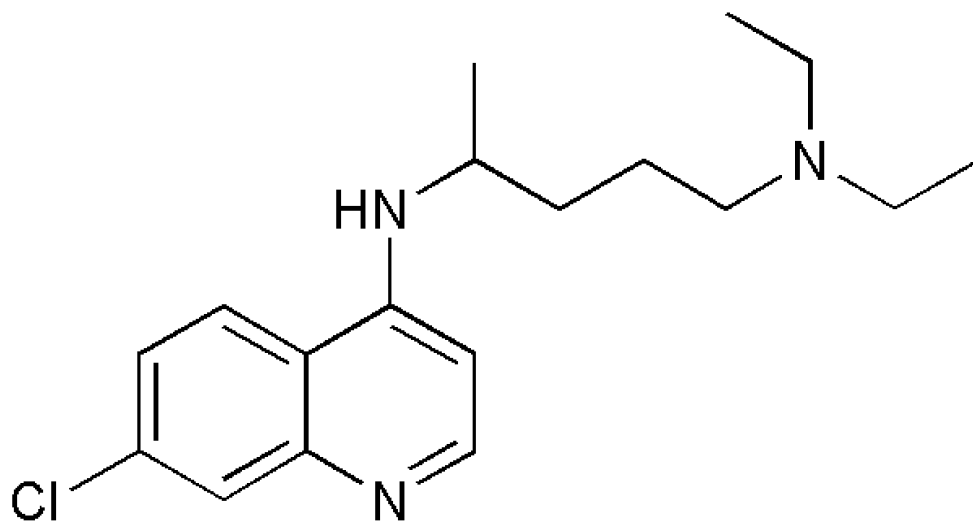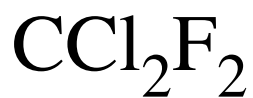# BULLETIN FOR THE HISTORY OF CHEMISTRY

Division of the History of Chemistry of the American Chemical Society

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# BULLETIN FOR THE HISTORY OF CHEMISTRY

# VOLUME 31, CONTENTS

*The Cover*…Chemicals that have made history
See pp 66, 75.

# THE ROLE OF THEORIES IN EARLY STUDIES OF CHEMICAL EQUILIBRIA

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This work traces the role of theories of chemical equilibria that evolved around different research programs concerning the attempts at measuring chemical affinities. We will concentrate on searching for the theoretical grounds of four basic chemical equilibrium concepts: 'incomplete reaction,' 'reversibility.' 'equilibrium constant,' and 'molecular dynamics.'

Despite the fact that 'affinity' was the key concept for the development of the chemical equilibrium idea during the last quarter of the 18th century and 19th century (1), we will show that the concept was not given a precise definition. To its vague and ambiguous meanings we must add its polysemy (2). Kim (3) has noted that "the concept of affinity was rendered in many different ways, depending on the particular kind of practice that the chemist was engaged in." Therefore, we will discuss how scientists tried to determine the factors affecting affinity and how they tried to measure this property of chemicals, all of which led eventually to both mathematical reasoning and molecular dynamics as key theoretical tools in the explanations given to equilibrium reactions.

## Affinity Tables

The oldest tradition that explained why bodies or substances reacted was based on an anthropomorphic view of nature, for it established that chemical reactions were due to the concepts of sympathy and antipathy between substances, possibly being traced back ultimately to Empedocles's principles of 'love and strife' (4). The first idea of affinity as a term expressing the tendency of substances to react was introduced by Albertus Magnus. This concept stated that "the greater the affinity (resemblance, similarity, or relationship) between two bodies, the greater is their tendency to react." This view of the interaction between bodies occurring most easily between closely related substances ('like assorts with like') is an idea that goes back to Hippocrates (5).

In the early years of the 18th century, Newton tried to address a theoretical explanation for why some substances reacted with others. In the thirty-first Query of his book *Optics* he considered that in chemistry there would be forces similar to the gravitational ones. These forces were manifested only at a very short distance, and it was assumed that the extent of those forces depended on the type of substances involved. Within this theoretical basis, Newton introduced a mechanical view for chemistry. As a consequence, some scientists tried to give account of the measure of these 'elective affinities.' Buffon, Guyton de Morveau, and Bergman were some of the eighteenth-century chemists who supposed that chemical affinity was merely gravitational attraction, modified by the shapes of the small particles of the reacting bodies (6).

The chemists of the 18th century, either under the Newtonian paradigm or with the aim of systematizing all the known chemical behavior, began the construction of the first affinity tables. It was, essentially, an attempt at estimating the comparative differences in the

reactivity of bodies. The earliest affinity table ('Table des rapports') was published by E. F. Geoffroy in 1718 (7).  This table consists of sixteen columns. At the head of each column is the traditional symbol of a substance (or a group of substances to which it refers). Below it are the symbols of the substances with which it reacts, arranged in decreasing order of their affinity. Therefore, each substance will displace from combination any of those below it (8):

> Whenever two substances which have some disposition to unite, the one with the other, are united together and a third which has more rapport for one of the two is added, the third will unite with one of these, separating it from the other.

Geoffroy intended his table as a place where one could see at glance the different relationships between the principal materials with which one is accustomed to work in chemistry. He wrote (9):

> I have believed that it would be very useful to mark those relations which the substances commonly met with in chemistry show to each other and to construct a table where at a glance one could see the different relations which substances have for one another.

The affinity table then visually represented the relationships between chemical substances determined in the laboratory.  That is, it had two intended uses: to 'discover' what went on in the mixtures of several bodies and to 'predict' what had to result from them (10). Thus, the table represented a helpful device to both beginners and experienced chemists (11):

> By this table those who are beginning to learn chemistry may form in a short time an adequate idea of the rapports which exist between different substances, and the chemists will there find an easy method to determine what takes place in many of their operations which are difficult to disentangle and to predict what should result when they mix different bodies.

It is interesting to note how Geoffroy organized his table (12).  At the top of the left half of it, he listed three mineral acids and four different kinds of alkalis that produced a variety of middle salts with the substances below each of them; column 8 showed the reactions of metallic substances with individual mineral acids. Columns on the right half of Geoffroy's table were headed by sulfur, mercury, lead, cooper, silver, iron, antimony, and water. Klein (13) has explained that this section of the table derived largely from the age-old metallurgical practices which dealt with metallic sulfides (column 9), amalgams (column 10), and alloys (columns 11-15).

There are conflicting interpretations of this first affinity table. Although some authors consider that Geoffroy's table embodied Newtonian philosophy, it is difficult to prove any influence of Newtonian matter theory on the table (14).  Holmes (15) suggested the (mysterious) term 'rapports' was a convenient device to avoid the complications of the 'ad hoc' mechanistic images held by other members of the 'Academy of Sciences.'  This does not mean, however, that the table was a nontheoretical, merely empirical, theory-neutral 'art' rather than science.  Kim (10) reported a historiographical analysis confronting that empiricist assumption. Holmes (16) has identified salts as the main subject of theoretical investigation in eighteenth-century chemistry and placed Geoffroy's affinity table in the midst of it.  Not only did the table depict middle salts as combinations of acids and bases, but it rested on the premise that chemical composition was determined by rapports of affinities. Also, the selective displacement of metals in acids emerged as a central question in theoretical chemistry. Holmes has stressed that the table of rapports was not simply a classification of experimental evidence, summarizing chemical reactions and predicting others, for it represented ways to view and to organize that knowledge and to set priorities for further investigation. Moreover, Klein (17) has argued that the modern concept of the chemical compound provided the conceptual framework for Geoffroy's table.

Geoffroy employed in his table the term 'rapport' to indicate the 'dispositions' of substances to unite (18), in contrast to the meaning of 'affinity,' which carried a somewhat ambiguous connotation of kinship and analogy. Still, this early meaning as the cause of chemical combination was gradually replaced by the words 'affinity' and 'attraction' in the late eighteenth century. In practice, affinity and attraction were virtually identical, signifying the 'tendency to combine,' which meant that 'affinity' gradually lost its connotation of cousinly relationship; and, likewise, 'attraction' lost any implication of a particular kind of mechanical explanation (19).

Thus, Kim suggested that chemical affinity developed as a viable investigative program because of its function in guiding laboratory practice, rather than because its claim embodied Newtonian philosophy. She stated (20):

> Geoffroy's 'rapports' served on the one hand to classify chemical substances and on the other hand as an umbrella term referring to the cause of chemical combination. His table of 'rapports' recorded the observed relations between chemical substances

without the speculation on the indivisible principles or particles that supposedly underlay the phenomena. Such avoidance of metaphysical speculations was closely linked to the formulation of affinity chemistry as a laboratory science.

During the decades after 1720 Geoffroy's conceptual structure began to expand, as chemists applied it and the solution methods with growing power to discover new combinations within each of the categories of acid, alkali, alkaline earth, and metal (21). Although many chemists contributed to the elaboration of tables of chemical affinities, the Swedish chemist T.O. Bergman made the most extensive studies of displacement reactions. He published in 1775 *De Attractionibus Electivis*. This table, as well as those that followed up until 1784, was constructed with the aim of studying all the possible reactions. Bergman's theoretical goal was to discover by experiment the order of the varying attractions between different particles. This attraction, following very different laws from the gravitational forces, depended on the positions and figures of the particles. Thus, this conceptual framework established that chemical combinations were the result of the 'elective affinities,' which solely depended on the nature of the substances involved in the reaction. The determination of the affinities gave a relative order, which accounted for the interpretation of displacement reactions. He stated (22):

> Suppose $A$ is a substance for which other different substances $a$, $b$, $c$ have an attraction; suppose further, $A$ combined with $c$ to saturation, (this union I shall call $Ac$), should upon the addition of $b$, tend to unite with it to the exclusion of $c$, $A$ is then said to attract $b$ more strongly than $c$, or to have stronger elective attraction for it; lastly, let the union of $Ab$, on the addition of $a$, be broken and let $b$ be rejected, and $a$ chosen in its place, it will follow, that $a$ exceeds $b$ in attractive power, and we shall have a series, $a$, $b$, $c$, in respect of efficacy. What I here call attraction, others denominate affinity.

Therefore, an acid replaced another one if its affinity toward a base were greater than the one initially combined with the base. Another field of application was the interpretation of the dissolution of metals.

Bergman considered all reactions as being complete and taking place in only one direction. However, he was aware of other factors that also affected chemical transformations: the possibility of evolution of gases depending on the temperature; the varying solubility of substances; and the influence of the mass of the substances over the course of the reaction. Bergman did not believe that any influence other than heat could mask the

forces of affinities. Therefore, he felt that few remaining anomalous reactions resulted from inadequate data, believing that further and careful experimentation would enable chemists to fit all reactions into ordered displacement affinity series without inconsistencies (23). On the contrary, new anomalies, the result of the initial amounts of the reactants, solubility of substances, or their volatility, were reported, although they were initially considered as external factors that could counteract the true relative order of affinities.

Eventually, affinity tables summarised visually the reactions between substances and thus allowed a certain degree of prediction; the table served as the theory. Hence, it can be asserted that the device of Geoffroy's table initiated a tradition from which to formulate empirical laws that would make chemistry respectable and might eventually even be expressible mathematically. Bergman, in his *Dissertation on Elective Attractions*, stated (24):

> In this dissertation I shall endeavour to determine the order of attractions according to their respective force; but a more accurate measure of each, which might be expressed in numbers and which would throw great light on the whole of this doctrine, is as yet a desideratum.

In accordance with this purpose, several authors attempted to determine the magnitude of the force of affinity or chemical attraction. Wenzel, Kirwan, Guyton de Morveau, and Fourcroy were some of the most prominent chemists who adhered to this tradition (25). Wenzel believed that the order of affinity of metals for a solvent that would dissolve them bore an inverse relationship to the time required for their dissolution. In other words, affinity was regarded as a force and the body acted upon as a resistance; thus, the velocity of dissolution was considered to be proportional to the force and inversely proportional to the resistance. Fourcroy rejected the idea that the velocity of combination was the measure of affinity, for the time needed for a combination could not express the force. Kirwan concluded that the weights of bases required to saturate a determinate weight of an acid were in direct relation to the affinities of the acid for the bases. Guyton de Morveau attempted to measure the attractions between metals and mercury by the force required to detach metal discs floating on mercury.

## Berthollet and the Importance of the Amounts of the Reactants

At the end of the 18th century, the concept of affinity was consolidated as a coherent system for explaining chemi-

cal reactions. It was assumed that affinity was a constant property of the substances and that it manifested itself in an elective way. According to this conceptual framework, chemical reversibility was forbidden because it was assumed impossible that a reaction whose direction was determined by the relative order of affinities could be reversed. Those reactions which, under some particular conditions, deviated from the order established by the table became anomalous problems, somehow to be integrated into the theoretical framework of elective affinities (26). Indeed, the problem of incomplete and reversible reactions was already known to chemists before the French Revolution. At the beginning of the 19th century, those unusual reverse reactions were given a new explanation by the French chemist C. L. Berthollet.

Berthollet, who was a professor of Chemistry at the École Normale, initially adhered to the paradigm of elective affinities, although he was aware that some decades earlier Macquer, Kirwan, and Guyton de Morveau had extensively discussed and puzzled over the reactions that contradicted the invariability of affinities (27). From this previous knowledge, the social demand for pure nitre, and the teaching program Berthollet had developed at the École Normale, he was prompted to revise the concept of elective affinities (28).

We must place the work of Berthollet in the socio-political context that followed the French Revolution. In 1789 he faced the problem of the invariability of affinities when trying to find a reliable test for the determination of the purity of nitre. The anomalies he found in dealing with this problem reappeared four years later when he was appointed director of a refinery of nitre for the production of gunpowder. To obtain pure $KNO_3$ required some recrystallizations and Berthollet took into account that as the concentration of nitrate increased, the capacity of the solution for dissolving additional nitrate decreased. He interpreted this anomaly by stating that the affinity responsible for dissolution was not an absolute force; therefore, in this phenomenon there would be an equilibrium between antagonistic forces.

Berthollet had to organize all this new knowledge for his classes at the École Normale.  The effect of the proportions of substances was not an anomaly anymore. It challenged the previous theory, for the result of the amount of substances was irreconcilable with the principles of elective affinities. Moreover, Berthollet's ideas, which were developed from experiences with chemical reactions on a large scale (29), had a new frame of implementation thanks to the trip he made in 1798,

when he accompanied Napoleon's expedition to Egypt (30). He observed the continuous formation of sodium carbonate on the edge of 'sodium lakes.'  This reaction can be represented as follows:

$$CaCO_3 + 2\,NaCl \rightarrow CaCl_2 + Na_2CO_3$$
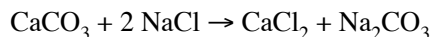
This reaction was the reverse of that predicted by the theory of elective affinities. Berthollet accounted for it by means of the great quantities of sodium chloride and calcium carbonate present and the continuous removal of the products: in point of fact, the sodium carbonate formed a crust around the edge of the lake, and the deliquescent calcium chloride seeped into the ground.

When he returned to France, Berthollet published his findings in several journals and in two books: *Recherches sur les lois affinités chimiques* (1801) and *Essai de Statique Chimique* (1803).  Berthollet's aim was to refute the notion of elective affinity, although he did not deny the action of affinities as the cause of chemical combination (31):

> The immediate effect of the affinity which a substance exerts is always a combination, so that all the effects which are produced by chemical action are a consequence of the formation of some combination.

He called attention, however, to the mass as one of the factors affecting the result of a reaction (32):

> All substances which tend to enter in combination act by reason of their affinity and their quantity.

That is, Berthollet objected to the sense of false absoluteness that the notion of elective affinity conveyed, adding the effect of quantity on chemical action, for the mass of the reactants could reverse the reaction predicted by the scale of relative affinities. Thus, if two substances are competing to combine with a third substance for which they have unequal affinities, a relatively large quantity of the substance with weaker affinity may exert a force that can surpass the force of  the substance with greater affinity. Hence, Berthollet objected to the perception that elective affinity was an absolute, constant force that always determined the outcome of displacement reactions. He wrote (33):

> The doctrine of Bergman is founded entirely on the supposition that elective affinity is an invariable force and of such a nature, that a body which expels another from its combination, cannot possibly be separated from the same by the body which it eliminated. Such was the certainty with which elective affinity has been considered as a uniform force, that celebrated chemists have endeavoured to represent by numbers, the comparative elective affinities of different substances,

independently of any difference in the proportion of their quantities.

It is my purpose to prove that elective affinity, in general, does not act as a determinate force, by which one body separates completely another from combination; but that, in all the compositions and decompositions produced by elective affinity, there takes place a partition of the base, or the subject of combination, between the two bodies whose actions are opposed; and that the proportions of this partition are determined, not solely by the difference of energy in the affinities, but also by the difference of the quantities of the bodies; so that an excess of quantity of the body whose affinity is weaker compensates for the weakness of the affinity.

If I can prove that a weaker degree of affinity can be compensated by an increase of quantity, it will follow, that the action of any body is proportionate to the quantity of it which is necessary to produce a certain degree of saturation. This quantity, which is the measure of the capacity of saturation of different bodies, I shall call *mass*.

Hence it follows, that in estimating the comparative affinities of bodies, their absolute weights are to be considered, and ought to be equal; but in comparing their actions, which depend on their affinities and mutual proportions, the mass of each is to be considered.

Moreover, in a recent study, Kim has focused her attention on the central goal of Berthollet's *Recherches*. She has stressed that (34):

For Berthollet chemical affinity possessed a mechanical component, for the force of affinity was proportional to the mass of the reactant.

He stated (35):

The forces which produce chemical phenomena are all derived from the mutual attraction between the molecules of the bodies and have been given the name *affinity*, to distinguish it from astronomical attraction. ...the effects of chemical attraction, or affinity, are affected by particular conditions, often indeterminate, that a general principle cannot be deduced....However, since it is very probable that affinity does not differ in its origin from general attraction, it should equally be subject to the laws which mechanics has determined for the phenomena due to the action of mass, and it is natural to think that the more the principles to which the chemical theories apply have generality, the more they have analogy with those of mechanics; but it is only by observation that they can reach that degree which they are already able to indicate.

Berthollet considered that any displacement reaction was never complete but that there was an equilibrium state between opposite affinity forces. The strength of these forces, therefore, depended on two factors: the difference in their relative affinities and the quantitative proportion. The equilibrium state was, in a manner analogous to mechanics, static. Moreover, the extent of a chemical reaction was determined by the physical state of the reactants because it might affect the degree to which the affinities could play a role. Many reactions take place in solution, so if a product is an insoluble solid or a gas, it cannot exert its affinity over the dissolution, because its active mass decreases as it leaves the solution. This explanation accounted for the fact that many reactions continue to take place until at least one of the reactants is depleted.

The new conception modified the previous idea of elective affinity and deprived it of the leading role that it had played during the 18th century. The emphasis was now redirected to the concept of 'chemical action,' understood as the tendency between two substances to form a new combination, exerted according both to their relative affinity and their proportional amounts. Thus, the consideration of the mass of the reactants as a key factor provided a rationalization for incomplete reactions.  It also explained why both the "direct" (forward) reaction (permitted, according to elective affinities) and the reverse one (forbidden by that theory) could occur.

Berthollet's theory was not free of flaws and difficulties. M.G. Lemoine (36) drew attention to facts that contradicted Berthollet's laws such as the reactions in which soluble salts were formed from insoluble ones and the decomposition of substances by the action of gaseous acids and bases. The difficulties that Berthollet's ideas faced can be summarized as follows:

a)  The high level of acceptance of the theory of elective affinities among his contemporary chemists; this theory persisted during some decades as theoretical support for experimental investigations (37).

b)  The inherent difficulty of the new ideas, which meant that they could not be fully understood (38).

c)  The emergence of the atomic theory of Dalton and the electrochemical theory of Berzelius (39).

Berthollet's conception of affinity had an important corollary. Since affinities were a manifestation of universal attraction, all particles exerted an attraction toward all others, tending to unite them in chemical combination. Hence, combinations between particles in variable proportion were likely. This last assertion was inconsistent

with Dalton's new atomic theory, which established the principle of definite proportions.  As a consequence, the attention directed toward the determination of atomic weights and the composition of chemical compounds impeded a proper development of Berthollet's theory.  In addition, textbooks did not tend to present the theoretical basis suggested by Berthollet, and his ideas had to compete with the influence of Fourcroy and his school, which supported the theory of elective affinities (40).

Berthollet's measure of chemical action was "chemical mass," defined as the product of the quantity of the substance with the strength of its affinity.  He stated (41):

> I consider that each of the acids which compete for an alkaline base acts in proportion to its mass [that is, quantity multiplied by affinity]. In order to determine the masses, I compare the capacities of saturation, whether of all the acids with one base, or of all the bases with one acid.

The "strength of affinity" was equivalent to the "power of saturation" (42):  that is, the smaller the amount of acid required to neutralize a given quantity of base, the greater the affinity. But, it must be noted that this is nothing more than the equivalent weight.  Hence, Berthollet measured chemical action by dividing the amount of the substance by the equivalent weight, this quotient representing the number of equivalents of the substance taking part in the reaction. Berthollet hoped that his method would establish the relative affinities of acids and bases and thus that his theory eventually would supplant Bergman's determinations of affinities. Once his method had been shone to be invalid, it was thought that affinities could not be measured at all (43). However, at the beginning of the second half of the 19th century the interpretation of new experimental observations allowed the reformulation of his ideas. The new theory had mathematical support, which, its authors stated, finally allowed for the quantification of chemical affinities.

## The First Mathematical Formulation of Chemical Equilibria:  The Work of Guldberg and Waage

Between the time of publication of Bethollet's *Essai* and the year 1864 the problem of the affinity had not developed substantially (44). Only in the last third of the nineteenth century did chemists turn their attention to the theory of affinity, which could then evolve in the light of new kinetic and thermodynamic ideas (45).

As discussed above, early investigations of chemical affinity focused primarily on acid/base and metal/acid reactions. Berthelot's laboratory practice redefined affinity studies by focusing on organic equilibrium systems and slow reactions. In 1862 Berthelot and Saint-Gilles used a new experimental approach to the study of reactions in solution. They thought that reactions between acids, bases, and salts were not appropriate in the study of chemical equilibria because they were so fast that any analytical technique upset the equilibrium. These disadvantages were overcome by turning to the study of esterification reactions, whose rates were sufficiently slow. Besides, the amounts of each component at equilibrium were always high enough to be easily measured. Berthelot and Saint-Gilles had established that the amount of ester formed at any instant was proportional to the product of the reacting substances (*i.e.* alcohol and acid) and inversely proportional to the volume. They also found that the reaction did not reach completion but progressively approached a limiting situation (*i.e.* equilibrium), where all four substances were present simultaneously. Berthelot and Saint-Gilles devised a mathematical formulation of the phenomenon but failed to take into account the reverse reaction between ester and water.

Berthelot's and Saint-Gilles's experimental findings were the starting point for the investigations performed by two Norwegian scientists, C. M. Guldberg and P. Waage. Their own experimental work was concerned with a heterogeneous system, the reaction between solid barium sulfate and a solution of potassium carbonate, together with the reverse reaction between solid barium carbonate and potassium sulfate solution. They tried to formulate a general mathematical equation to account for the experimental data, with the aim of devising a theory that could reconcile the earlier ideas of Bergman and of Berthollet. In their first work of 1864 (46), taking into account mechanics as a paradigm, they focused on the measurement of what was responsible for what they called "chemical forces." Convinced that chemistry should become, like mechanics, a science of forces and their effects, Waage and Guldberg aspired to develop a mathematical theory of chemical affinity.  For a process they called simple (which we can represent as A = B + C), they stated (47):

> …two forces assert themselves, either a composing or a decomposing, or an acting and reacting, and we view it as unavoidably necessary to regard these forces together if one is to find any quantitative expression of these forces.

Unlike Berthollet, Guldberg and Waage assumed that chemical forces were not proportional to the amounts of the substances involved in the reaction, but to the "active masses" (concentrations). For each substance, its active mass had a power they determined by experiment. Thus, for the following:

$$P + Q = P' + Q'$$
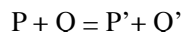
they argued as follows (48):

> If one begins with the general system which contains the four active substances in a variable relationship and designates the amounts of these substances, reduced to the same volume by p, q, p', and q', then, when the equilibrium state has occurred, a certain amount x of the two first substances will be transformed. The amounts of P, Q, P', and Q' which keep each other in equilibrium will be consequently $p - x$, $q - x$, $p' + x$, and $q' + x$ respectively. According to the law of mass action, the force for the first two substances is $\alpha(p - x)^a(q - x)^b$ and the action force for the last two is $\alpha'(p' + x)^{a'}(q' + x)^{b'}$ [where $\alpha$ and $\alpha'$ were proportion constants and *a* and *b* exponents, all to be determined by experiment]. Hence, the equilibrium is expressed as:
>
> $$\alpha(p - x)^a(q - x)^b = \alpha'(p' + x)^{a'}(q' + x)^{b'}$$

For the equilibrium :

> acetic acid + ethanol = ethyl acetate + water
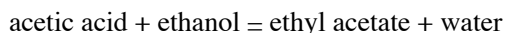
they obtained the following results:
a = 1; b = 0.786; a' = 0.846; b' = 0.807; $\alpha/\alpha'$ = 0.502.

We must stress that Guldberg and Waage obtained an equilibrium equation that represented a balance between two "chemical forces."  In their memoir of 1867 (49), for the reaction A + B = A' + B' they expressed the force as k·p·q, where k is the coefficient of affinity and p and q are the active masses of A and B. Similarly, they expressed the force which produced A and B from A' and B' as k'·p'·q', where p' and q' are the active masses of A' and B'. When the two forces are in equilibrium, the active masses remain unchanged, and k·p·q = k'·p'·q'. They reasoned as follows:

> If the number of molecules A, B, A' and B' before of the reaction be represented by P, Q, P' and Q', and if x be the number of molecules of A and B transformed into A' and B', then, supposing the total volume to remain constant during the reaction, we have

$$p = \frac{P - x}{V}, \quad q = \frac{Q - x}{V}, \quad p' = \frac{P' + x}{V}, \quad q' = \frac{Q' + x}{V}$$

and by substituting these values in the equation of equilibrium and multiplying by $V^2$, we get the general equation

$$(P - x)(Q - x) = \frac{k'}{k}(P' + x)(Q' + x)$$

This formula received confirmation from previously published research by Berthelot and Saint-Gilles. Moreover, the accuracy of the above equation was tested by Thomsen in 1869 and later by Ostwald in 1876 (50). Also, Guldberg and Waage's mathematical treatment enabled determinations to be made of the ratio k'/k; that is, of the relative affinities of two substances for a third with which both interact, and more particularly of the relative affinities of two acids for the same base, and of two
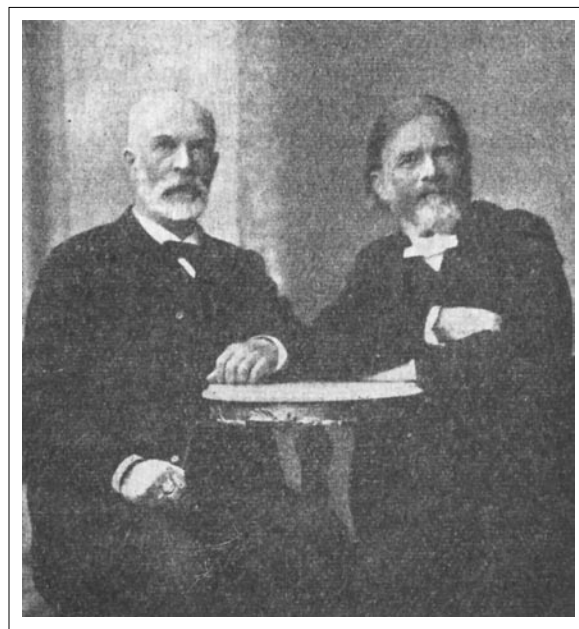


*Only known image of Guldberg (l) and Waage (r). See Ref. 5, Vol. 4, 1964, p 588*

bases for the same acid. This idea was further developed experimentally by Ostwald (51).

## Dynamic Equilibrium

In 1753 the *Encyclopédie* contained the article "Chymie" written by G. F. Venel. His purpose was to liberate chemistry from the yoke of physics (52). Venel's discussion demarcated the chemical side of the boundary between chemistry and physics. To achieve this end he devised

an adynamical theory of reaction. This theory supposed that reactions were instantaneous and thus they lacked the temporal element of Newtonian mechanics. Therefore, the program embodied in Newtonian affinities stood in opposition to the legacy of Venel's efforts to root dynamics out of chemistry.

The first systematic idea about time in chemical reactions was formulated by C. F. Wenzel (53), whose aim was to search for a method of measurement of chemical affinities. By analogy to mechanics, he chose to measure chemical forces by the velocities with which they affected analogous processes. In his 1777 book on affinity, entitled *Theory of the Affinities of Substances*, he described some measurements of the rates of the dissolution of metals in acids. He found that the rate at which metals were dissolved was influenced by the concentration of the acid as well as by the nature of the acid. As his goal was to estimate chemical affinities, he concluded that the affinity of substances to a common solvent was inversely related to the time of dissolution. Hence, he concluded that the quicker the action of the solvent the greater was the degree of its affinity.

In the summer of 1864 Guldberg and Waage presented a paper in which they argued in terms of the velocities of reactions in forward and reverse directions. They derived the following rate equation for the forward reaction (54):

$$v = \frac{dx}{dt} = k(p - x)^a (q - x)^b$$

where *v* is the velocity of reaction, *x* is the quantity transformed in the time t, and *k* a constant depending on the nature of the system, including the temperature. Similarly, they also considered the rate equation for the reverse reaction. The rate of the net reaction was considered to be the difference of the two velocities (*i.e.* $v_{net} = v_{forward} - v_{reverse}$). And, thus, they defined the equilibrium condition: $v_{net} = 0$. Although Guldberg and Waage later argued in terms of the "rates" of reactions in forward and reverse directions, initially they did it in terms of "forces." This assumption can be found in the eighth section of their second publication (55):

> When two substances A and B are changed into two new substances A' and B', we call the quantity  of A' + B' which is formed in unit time the *velocity* of the reaction, and we establish the *law that the velocity is proportional to the total force of A and B*. Assuming that the new substances  A' and B' do not react on one another, we shall have

$$v = \phi \, T,$$

where v is the velocity, T is the total force, and $\phi$ is a coefficient which we call *coefficient of velocity*. The velocity represents the *total force* and we can determine this force in the reactions  we can measure the velocity. Representing by *x* the quantities of A' and B' which are produced in the time t, it will be possible to express the total force, T, as a function of x, and noting that

$$v = \frac{dx}{dt},$$

it will be possible to determine *x* as a function of *t*. The equation which is found between *x* and *t* will serve to determine the *coefficients of affinity* and the *coefficients of action.*

When A and B react to give A' and B', and, at the same time A' and B' react to give A and B, the quantities of A' and B' formed in unit time are proportional to the difference of the two total forces. Consequently, the velocity is expressed by the equation

$$v = \phi \, (T - T')$$

When v = 0, then T = T', thus, the equilibrium is attained.

Laidler (56) stated that, although Guldberg and Waage's theory agreed with experimental data, they had not arrived at their mathematical expressions in anything like a satisfactory way.  Neither did they make any contribution to kinetics, since they worked in terms of forces and not of rates, although they did tentatively suggest that the rates might be proportional to the forces.  Guggenheim expressed his strong criticism as follows (57):

> ...to Guldberg and Waage belongs the credit of being the first to appreciate qualitatively the nature of a balanced reaction. But they did not succeed in formulating a quantitative expression for the equilibrium condition until six years after Horstmann had done so for gases and two years after van't Hoff had done so for the ester hydrolysis. They made no significant contribution either experimentally or theoretically to our knowledge of kinetics.

Ostwald had already remarked that a decisive step in the theory of chemical affinity was achieved only with the clear renunciation of the fiction of chemical forces. He stated (58):

> In chemistry, specially, the concept of force has only done damage. As long as one sought to measure chemical 'forces,' the theory of affinity made no progress. Indeed, one still finds the expression in Guldberg and Waage, but only to be soon eliminated. A more general and thorough-going understanding of

the laws of chemical affinity was first achieved when one made chemical energy and its transformation the object of research.

Still, the consideration of the concentrations of the substances involved in the equilibrium system, instead of their amounts (*i.e.* masses), was a key factor that accounted for the understanding of the evolution of chemical equilibrium. Moreover, the vital step neglected by Berthelot and Saint Giles, that of the reverse reaction, was taken into account by Guldberg and Waage, eventually allowing them to formulate the condition for chemical equilibria (v = 0). Finally, we would like to stress that the search for an exact mathematical relationship between the concentrations of the substances involved in equilibrium represented a promising starting point in the search for a quantitative determination of chemical affinities. Kim remarked that (59):

> The new status of mathematics in chemistry was partly due to its utility as an investigative tool…The evolution of mathematics from an investigative tool to theory was largely due to its utility in organizing numerical results, which otherwise were meaningless. In other words, the status of mathematics as a theoretical structure of physical chemistry developed hand in hand with the nineteenth century penchant for precision measurement.

Hence, in spite of their theoretical flaws, the importance of Guldberg's and Waage's equations has been noted by several authors (60).

As Servos (61) pointed out, Guldberg and Waage's work did not produce an immediate interest in the study of the law of mass action. Some of the publications in the 1870s might have given Guldberg and Waage the impression that their papers of 1864 and 1867 had not been generally known (62). They could have felt the need to write about their ideas in a more widely circulated journal (63). Only in this latter paper did Guldberg and Waage devise an equation similar to the equilibrium constant. In it, the exponents were the stoichiometric coefficients in the chemical equation representing the equilibrium system. Moreover, in this paper they referred to previous works by Thomsen, Ostwald, Horstmann, and van't Hoff (64) as a confirmation of their law of mass action.

During his tenure as professor at the Riga Polytechnicum (1882-1887), Ostwald turned his attention from equilibrium methods to ones based upon the measurement of reaction velocities (65). In 1883 he published a new series of papers on chemical dynamics, which was elaborated in full analogy to mechanics (66). Ostwald's

new research program was grounded on the manipulation of Guldberg's and Waage's dynamical equation to bring out his relative affinities. He stated (67):

> From the measurement of the velocities of chemical reactions we are enabled to solve the old problem of measuring the intensity of chemical forces. If two analogous substances (e.g. two acids) occasion under the same conditions analogous processes with different velocities, we shall attribute greater intensity of the chemical forces to the substance generating the greater velocity.

Eventually, a theoretical explanation of Guldberg and Waage's equations (68) came mainly from the works of van't Hoff (69). His ability to combine factors that had seemed unrelated by mixing traditions and manipulating ideas in new ways illustrates how the roles of imagination and creativity are important in the development and evolution of scientific knowledge (70). He turned his attention to the question of how the equilibrium state was reached. Thus, his interest was no longer on the static analysis of forces, but on the dynamics of rates of reversible reactions. The starting point of his deduction was that the equilibrium is to be regarded as a result of two processes taking place with the same velocity in opposite directions. Van't Hoff's kinetic approach in the derivation of the equilibrium constant is described in his book *Études de dynamique chimique*. This title has two features: its point of difference and its verbal similarity to Berthollet's *Essai de Statique Chimique*. That is, it serves to underline the differences as well as the roots of the new approach. Root-Bernstein (71) pointed out that van't Hoff, rather than worrying about what was formed as the end product at equilibrium as Berthollet had done, turned his attention to how the equilibrium state was reached. Root-Bernstein remarked (72):

> Van't Hoff always used experiment to prove an idea rather than in the hopes of discovering new phenomena in need of explanation. Experiment was for him a tool of testing, not a probe for investigating or discovering. For investigating and discovering things about nature, he used his imagination. ..Perhaps the diversity and extent of his teaching load help to explain the emphasis van't Hoff put on deducing the principles that governed chemical phenomena, rather than scrutinising the facts. He had neither the inclination nor the time to get bogged down in the latter. In this way, the demands of pedagogy shaped his research style, and the result was a book of chemical principles.

## Molecular Dynamics in Chemical Equilibrium

In the preceding sections attention has been called to the first attempts in the derivation of mathematical equations representing systems of chemical equilibrium. The brief historical account that follows here is intended to convey the early interpretations that accounted for how the equilibrium comes about.

In 1839 Gay-Lussac (73) imagined the equilibrium condition as a dynamic process of continuous interchange of acids and bases, which he described as a "pele-mele." Holmes suggested that this assumption (74):

> …probably made it more natural for chemists later to envision the equilibrium itself as a dynamic one involving the constant interchange of acid and base particles among the salt combination.

In the mid-19$^{th}$ century chemists paid increasing attention to the role of time in the course of chemical reactions (75). As mentioned in the previous section, the problem of chemical kinetics was closely linked with that of chemical equilibrium. In the following discussion we are going to enlarge that point on the basis of molecular considerations. In 1850 Williamson (76), studying the incomplete esterification reactions, was the first scientist to propose a submicroscopic model in order to explain the "static" state of chemical equilibrium. He did not consider this equilibrium as a situation in which nothing happens; on the contrary, he assumed that two reactions run simultaneously, each in opposite direction. Thus, reactants as well as products were constantly forming and decomposing in such a way that the amount of all the substances involved remains constant. This dynamic balance was achieved by assuming an interchanging of atoms, equal in absolute number in each moment of time, taking place in opposite direction. Consequently, the relative velocity of transfer of analogous atoms in each of the two directions was not the same, but it was greater for the substances of lower quantity.

A later attempt to explain the molecular changes taking place in an equilibrium state was due to Pfaundler. In an 1867 article he treated a chemical reaction in terms of the kinetic theory developed by Clausius and Maxwell. Pfaundler's approach was the first attempt to apply the mechanical theory of heat to chemical reactions (77). That is, Pfaundler used Clausius's kinetic theory of evaporation for the development of a qualitative theory of chemical dissociation (78). He was concerned with the problems arising when trying to apply Avogadro's hypothesis to the determination of molecular weights (79). According to that hypothesis there is a simple relation between the relative vapor density and the molecular weight. But this method met with great difficulties when it was applied to the case of ammonium chloride: the value of the vapor density of ammonium chloride was one half of that expected for the formula $NH_4Cl$. A partial decomposition was suggested in order to account for the experimental data; although most chemists of that time accepted this phenomenon, they could not provide an explanation.

Pfaundler was the first scientist who gave a correct account of partial dissociation. He hypothesized that the change varies in different molecules: a fraction of them is completely dissociated, and another fraction is unchanged. In the case of partial decomposition of a gas, Pfaundler assumed that at constant temperature and pressure equal amounts of molecules decompose and unite by collision. That explanation required that not all molecules were in the same state of motion at a given temperature. That is, it was assumed that some of the molecules regularly diverged more or less widely from the average state, for only a small number of collisions were effective to produce chemical reaction both in the sense of decomposition and formation. Eventually, a balanced molecular chemical equilibrium between decomposition and recombination was achieved.

In their last paper, Guldberg and Waage (80) took into account molecular kinetics and energy considerations. This was an attempt to explain the molecular changes taking place in an equilibrium state in the terms previously stated by Pfaundler in 1867. They reasoned as follows (81):

> If we consider a chemical process taking place under such circumstances that two substances A and B are converted into two others A' and B', while at the same time the reconversion of A' and B' into the original A and B can also occur, then the mere assumption of attractive forces between the substances of their components is no longer sufficient to explain the reactions, but we must for this purpose take into account the motion of the atoms and molecules.

> The equilibrium between two such chemical processes is a mobile equilibrium, for two opposite reactions take place simultaneously –fresh quantities of A' and B' being formed while A and B themselves are being reproduced. When equal quantities of these pairs are formed in unit time, equilibrium results. The chemical reaction for the conversion of A and B into A' and B' is represented by the equation

$$A + B = A' + B'$$

If the molecule A is composed of the atoms or molecules $\alpha$ and $\gamma$, these latter execute their own proper movements within the compound molecules. Owing to these proper movements, $\alpha$ and $\gamma$ will now approach, now retire from each other, and under certain circumstances their motions will become of such extent as to decompose the molecules  A into the two components $\alpha$ and $\gamma$. The same holds for $\beta$ and $\delta$, the components of the molecules B.

$$A = \alpha + \gamma \text{ and } B = \beta + \delta.$$

Now, as each of the compound molecules A and B is in motion as a whole, it will from time to time come to pass that a molecule A will encounter a molecule B. If this encounter of A and B happens under such circumstances that either $\alpha$ and $\gamma$ as well as $\beta$ and $\delta$ are completely separated from each other, or at least that the distance between $\alpha$ and $\gamma$ on the one hand, and between $\beta$ and $\delta$ on the other, has almost reached the boundary of the sphere of action, the chemical forces of attraction between $\beta$ and $\delta$, and between $\alpha$ and $\gamma$ can do no other than condition the formation of two new molecules A' and B', where A' = $\alpha$ + $\delta$ and B' = $\beta$ + $\gamma$. In the same way an encounter of two molecules A' and B' may cause the formation of A and B, if the components $\alpha$ and $\delta$, on the one hand, and $\beta$ and $\gamma$, on the other, are either completely separated or so far removed from each other that the attractive forces between $\alpha$ and $\gamma$ and between $\beta$ and $\delta$ are capable of effecting the formation of new molecules.

The rate of formation of new substances may be determined in the following way. If the number of molecules A and B in unit volume be denoted by p and q, the product pq will represent the frequency of the encounters of these molecules. If now each motion of the various molecules be equally favourable to the formation of new substances, the velocity of the chemical reaction –in other words the quantity transformed in unit time– may be made equal to $\phi pq$, the coefficient of velocity being supposed dependent on the temperature.

This view, already known from the theory of gaseous dissociation, may now be extended as follows so as to become generally applicable to all states of aggregation.

Amongst the p molecules of A in unit volume, there will be in general only a certain fraction of them, a, in such condition that on encounter with the molecules of B a chemical exchange will take place. Similarly, amongst the q molecules of B contained in unit volume, there will be only a fraction b in the state requisite for chemical exchange with the molecules of A. Thus on the whole there are in unit volume ap molecules of

A and bq molecules of B, which on meeting will be transformed into new substances. Consequently the frequency of encounter of the active molecules will be represented by the product ap·bq, and the rate at which the formation of new substances will proceed is to be expressed thus

$$\phi ap \cdot bq = kpq$$

if for brevity we put $\phi ab = k$.

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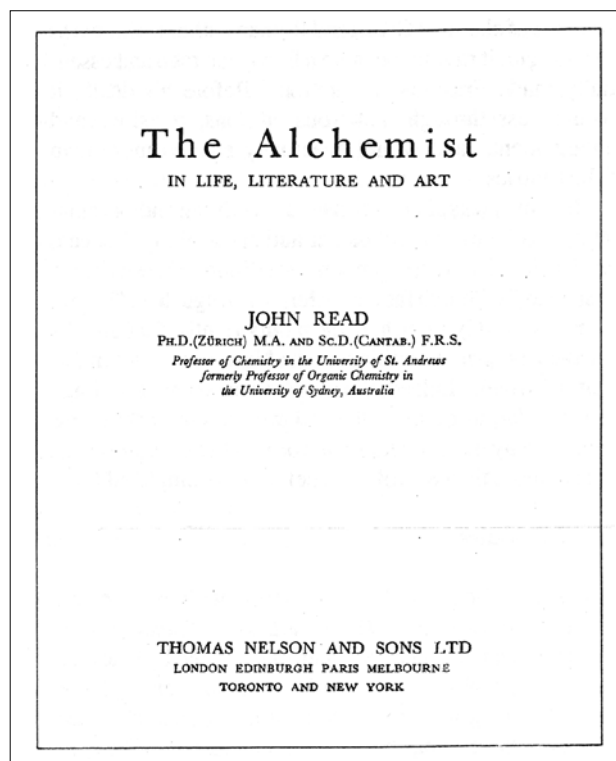
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# ERASMUS ON ALCHEMY*

William B. Jensen, University of Cincinnati

In 1947 John Read, Professor of Chemistry at the University of St. Andrews in Scotland and well-known authority on alchemy, published a slim volume entitled *The Alchemist in Life, Literature and Art* (1).  As indicated by the title, Read's intention was not to discuss the "internal" art and imagery of the alchemical literature itself but rather the "external" or cultural image of the alchemist as reflected in conventional European art and literature of the period 1300-1700.

In the case of art, Read dealt primarily with the paintings and prints of such 16th- and 17th-century Dutch and Flemish artists as Brueghel, de Bry, Teniers, Steen, and Wijck.  Many of these works are familiar to modern chemists, irrespective of whether they have an explicit interest in the history of chemistry, since reproductions of many of them adorn the conference rooms and hallways of modern chemistry departments, thanks to the generosity of both the Fisher Alchemical Collection and the private collection of Alfred Bader (2).  In the case of literature, Reid focused primarily on two works: "The Canon's Yeoman's Tale," found in Geoffrey Chaucer's (c.1342-1400) *Canterbury Tales*, which was probably written around 1391, and Ben Jonson's (c.1572-1637) comedy, *The Alchemist*, first published in 1612 but probably performed on stage as early as 1610 (3, 4).

Curiously absent from Reid's discussion is a third literary work dealing with alchemy by the famous Dutch humanist, Desiderius Erasmus (c.1467-1536). Also entitled "The Alchemist," this short dialogue first appeared in the 1524 edition of Erasmus' well-known work, *Familiar*



The Alchemist
IN LIFE, LITERATURE AND ART

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*Title page to John Read's 1947 monograph on* The Alchemist in Life, Literature and Art *(Oesper Collections).*

*Colloquies*—an extremely popular book, which was both widely read and widely translated throughout the 16th, 17th and early 18th centuries.  Indeed, not only did Read

fail to note the existence of this work (5), there is also no mention of it in the standard English works on alchemy by Taylor (6) and Holmyard (7), in the index to *Ambix* (the primary scholarly journal dealing with the history of alchemy), nor in the multivolume general histories of science and chemistry by Thorndike (8) and Partington (9).  Only Hermann Kopp's 1886 work, *Die Alchemie in Älterer und Neurer Zeit*, gives it a passing mention in the form of a two-sentence summary (10).  However, since the writing of the original draft of this introduction, it has come to my attention that Stanton Linden's 1996 literary study, *Dark Hierogliphicks: Alchemy in English Literature from Chaucer to the Restoration*, does provide a detailed summary of the tale, though this work, which was largely intended for historians of English literature, is unfortunately unknown to most historians of chemistry (11).  Despite this exception, the relative neglect of Ermasus' tale is readily apparent from the statistics found in Alan Pritchard's exhaustive bibliography of secondary works dealing with the history of alchemy, which contains 34 entries for Chaucer and 18 entries for Jonson, but none for Erasmus (12).

## Desiderius Erasmus

Born in either Rotterdam or Gouda, Holland, sometime between 1460 and 1470, Erasmus was ordained as a Catholic priest in 1492 (13).  However, he soon found the monastic life unbearable and instead contrived to make a living through a combination of teaching, editing, and writing.  His travels as an itinerant scholar would eventually take him to most of the countries of Europe and to England, where he would become a close friend of Sir Thomas More.

Most readers are probably familiar with Erasmus through an encounter with one of the many modern editions of *The Praise of Folly*, his famous satire on human weakness, vanity, and superstition, first published in 1511 (*Books in Print* lists no fewer than ten editions currently available).  However, this represents only a small fraction of his scholarly output.  He authored important textbooks on rhetoric and grammar and wrote extensively on humanistic education.  In 1500 he published a collection of pithy proverbs and adages culled from the writings of classical Greek and Roman authors.  Known as the *Adagia*, it rapidly became a European rage and essentially made Erasmus' reputation.  Before his death, it would pass through numerous editions, revisions, and enlargements, and would eventually contain more than 4,150 entries.

Erasmus was also responsible for editing and/or translating works by such classical authors as Pliny, Seneca, and Lucian; for his comprehensive editions of the writings of such early church fathers as Jerome, Augustine, Origen, Irenaeus, and Cyprian; and, most importantly, for publishing the first printed edition of the New Testament in the original Greek.  Indeed, the modern comprehensive English translation of his collected works, currently being published by the University of Toronto Press, promises to exceed more than 88 volumes before it is completed (14).



*Desiderius Erasmus of Rotterdam (c. 1467-1536). An engraving by Albrecht Dürer showing Erasmus in 1526, shortly after he composed his dialog on alchemy (Oesper Collections).*

## The Colloquies

First begun about 1498 in conjunction with his teaching activities, the *Colloquies* (from the Latin *colloquor,* meaning "to converse") were originally composed by Erasmus in order to provide students with entertaining examples of both conversational and written Latin.  An unauthorized edition of the *Colloquies* was first published in Basel in 1518, followed by an authorized, corrected

edition the next year.  Between 1519 and 1533 Erasmus would expand and revise the *Colloquies* no fewer than 17 times, so that, by the time of his death in 1536, the book would contain a total of 61 dialogues.  The nature of the dialogues themselves also gradually evolved over time, becoming increasingly satirical and pointed in their portrayal of the mores and foibles of early 16th-century society.

As already noted, the dialogue entitled "The Alchemist" was first added by Erasmus to the *Colloquies* in 1524.  Set as the story of the duping of a wealthy dignitary named Balbinus by an anonymous priest posing as an alchemist, it is related in the form of a gossip-laden conversation between two old friends named Philecous and Lalus.  Though its general theme—the alchemist as con man—is essentially identical to that of the Yeoman's Tale related 133 years earlier by Chaucer, the details of the two stories are quite different.  Chaucer makes a great show of his technical knowledge by reciting lists of laboratory reagents, apparatus, and procedures.  In his version, the victim, rather than the alchemist, is a priest and is not only taken into the alchemist's laboratory, but is also allowed to assist in the laboratory operations. Using a powder of his own making, the alchemist successfully transmutes both mercury and copper into silver for his victim, each time introducing the silver by a ruse of some sort (e.g., silver filings secreted in a hollowed coal, in a hollow stirring rod, etc.) while simultaneously distracting his dupe.  In the end, the priest, convinced that the alchemist's powder works, purchases it for a sum of money and the alchemist departs.

In Erasmus' version, the technical details of the laboratory operations and the use of alchemical terminology are minimal.  Instead the emphasis is on the psychological details of how the alchemist manipulates his victim's greed and vanity and in detailing the many ploys which he uses in order to explain away his lack of success in the laboratory and to extract ever greater sums of money from his dupe (e.g., gold is needed to seed or attract fresh gold; the charcoal and other chemicals are impure or of the wrong variety; the glassware is defective; improper prayers are used; threats are made of imprisonment for the illegal practice of alchemy, etc.).  Indeed, though the alchemist goes through the pretense of setting up a laboratory, it is doubtful whether he ever performs any actual laboratory work.  In this respect Erasmus' tale is closer in spirit to the more elaborated version that would be given by Jonson 86 years later, than it is to that of Chaucer. Though there is a great display of alchemical terminology in Jonson's play, there is no real labora-

tory, as the alchemist and his assistant are temporarily operating out of the house of a wealthy homeowner, who happens to be away in the country.

## The Translation

Compared to the works of both Chaucer and Jonson, Erasmus' tale has the twin advantages of brevity and less antiquated English usage (depending, of course, on the age of the English translation)—virtues which make it a tempting, albeit less challenging, choice for use as a supplementary reading in an introductory history of chemistry course.  There are three English translations of the complete *Colloquies* to choose from—the first made by Henry Munday in 1671 (15), the second by Nathan Bailey in 1725 (16), and the third by Craig Thompson in 1965 (17) —as well as numerous translations of selected *Colloquies*.  Since the dialogue is apparently relatively unknown among chemical historians, we have chosen to append a typical English rendition for the use of teachers and students based on the 1902 translation made by Merrick Whitcomb of the University of Cincinnati Department of History, which is, in turn, based largely on the 1725 translation of Bailey (18).

## REFERENCES AND NOTES

\* One of the original purposes of the *Bulletin for the History of Chemistry* was to publish not only scholarly articles related to the history of chemistry, but also occasionally to reprint primary documents and translations that might be of interest to its readers. Hence, the reason for publishing the following translation of the little-known satire on alchemy by the 16th-century humanist, Desiderius Erasmus, for which Dr. Jensen has provided a brief introduction.

1. J. Read, *The Alchemist in Life, Literature and Art*, Nelson, London, 1947. Read received the 1959 Dexter Award for his contributions to the history of chemistry.
2. It is obvious in reading Read's book that he hoped that these external cultural images would also cast some objective light on actual alchemical practice. As a consequence, he somewhat naively assumed that the art work, in particular, provided the viewer with actual first person representations of real alchemists and actual alchemical laboratories.  In fact, as Hill has emphasized, many of these paintings are really imaginary artistic interpretations rather than objective "photographic" representations. The profusion of chemical apparatus—probably modeled on that of the local apothecary—found scattered about the floor in most of these paintings was designed to display the artist's virtuosity in the painting of complex still lives

rather than to accurately portray the state of chaos found in a typical working laboratory. For further details, see C. R. Hill. "The Iconography of the Laboratory," *Ambix*, **1975**, *22*, 102-110.

3. For a typical modern edition, see G. Chaucer, *The General Prologue to the Canterbury Tales and the Canon's Yeoman's Prologue and Tale*, Holmes and Meier, New York, 1976. For a modernized version, see F. E. Hill, *The Canterbury Tales Translated into Modern English Verse*, McKay, New York, 1965.

4. For a typical modern edition, see B. Jonson, *The Alchemist*, Yale University Press, New Haven, CT, 1974.

5. Nor is the dialogue mentioned in Reid's other works. See J. Read, *Prelude to Chemistry: An Outline of Alchemy, Its Literature and Relationships*, Bell, London, 1936, and J. Reid, *Through Alchemy to Chemistry: A Procession of Ideas and Personalities*, Bell, London, 1957.

6. F. S. Taylor, *The Alchemists: Founders of Modern Chemistry*, Schuman, New York, 1949.

7. E. J. Holmyard, *Alchemy*, Penguin, London, 1957.

8. L. Thorndike, *A History of Magic and Experimental Science*, Macmillan, New York, 8 volumes, 1923-1958. There are ten index entries for Erasmus in Vol. V and VI, which deal with the 16th century, none of which refers to his dialogue on alchemy.

9. J. Partington, *A History of Chemistry*, Macmillan, London, 4 volumes, 1961-1970.

10. H. Kopp, *Die Alchemie in Älterer und Neurer Zeit: Ein Beitrag zur Culturgeschichte*, Winter, Heidelberg, 1888, Part I, p 228. By way of contrast, no mention of Erasmus is found in E. O. Lippmann, *Enstehung und Ausbreitung der Alchemie*, Springer, Berlin, 1919.

11. S. J. Linden, *Darke Hierogliphicks: Alchemy in English Literature from Chaucer to the Restoration*, University of Kentucky, Lexington, KY, 1996, Chapter 3.

12. A. Pritchard, *Alchemy: A Bibliography of English-Language Writings,* Routledge and Kegan Paul, London, 1980. This also includes all articles appearing in *Ambix* prior to 1980.

13. A concise summary of the life and work of Erasmus can be found in J. McConica, *Erasmus*, Oxford University Press, Oxford, 1991. More detailed studies are listed in the bibliography of this volume.

14. *The Collected Works of Erasmus*, University of Toronto Press, Toronto, 88 volumes, 1974-present.

15. H. M. Gent. (H. Munday), *The Colloquies or Familiar Discourses of Desiderius Erasmus of Rotterdam, Rendered into English*, Brome et al., London, 1671.

16. N. Bailey, *All the Familiar Colloquies of Desiderius Erasmus of Rotterdam Concerning Men, Manners, and Things, Translated into English*, Darby et al., London, 1725.

17. C. R. Thompson, *The Colloquies of Erasmus*, University of Chicago, Chicago, IL, 1965. Reprinted as Vol. 39 and 40 of Ref. 14.

18. M. Whitcomb, *Select Colloquies of Erasmus*, University of Pennsylvania: Philadelphia, PA, 1902, 116-135.

## ABOUT THE AUTHOR

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## THE ALCHEMIST

### Desiderius Erasmus

*Philecous*: What's up that Lalus is smiling to himself, so that he almost bursts into a roar, making every now and then the sign of the cross? I'll interrupt his felicity. Good day, my dear Lalus; you seem to be very happy.

*Lalus*: But I shall be much happier when I have made you a partaker of my joy.

*Philecous*: Pray thee, then, make me happy as soon as you can.

*Lalus*: Do you know Balbinus?

*Philecous*: The learned old gentleman who enjoys such a fine reputation?

*Lalus*: The same; but no mortal man is wise at all times, or is without his weak side. This man, with all his good qualities, and they are many, is endowed with some blemishes. He has for a long time been bewitched with the art called Alchemy.

*Philecous*: Do not speak of it as a trifle, but as a dangerous disease.

*Lalus*: However that may be, and notwithstanding he has been so often deceived by this sort of people, he has lately suffered himself to be imposed upon again.

*Philecous*: In what manner?

*Lalus*: A certain priest went to him, saluted him with great respect, and accosted him in this manner: "Most learned Balbinus, perhaps you will wonder that I, a stranger, should thus interrupt you, who are, as I know, always deeply occupied with the most sacred studies." Balbinus gave him a nod, as was his custom, for he is wonderfully sparing of his words.

*Philecous*: That is an evidence of prudence.

understands the whole affair so well, that no man understands it better."

*Philecous*: You are sketching me an orator rather than an alchemist.

*Lalus*: You shall hear the alchemist by and by. "This good fortune," says he, "I have had from a child, that I learned that most desirable of arts, alchemy, the very marrow, I call it, of all philosophy." At the very mention of alchemy, Balbinus raised himself a little with an involuntary motion, then with a deep sigh bade him proceed. The priest continued: "But miserable man that I am," said he, "by not falling into the right way!" When Balbinus asked him what way



*The alchemist and his assistant, a woodcut by Hans Weiditz first published in 1532 but thought to have been done about 1520, thus making it almost exactly contemporaneous with Erasmus' dialog on alchemy (Oesper Collections).*

*Lalus*: But the other, as the wiser of the two, proceeds: "You will forgive my importunity when you learn the reason of my coming to you." "Tell me, then," says Balbinus, "but in as few words as possible." "I will," says he, "as briefly as I am able. You know, most learned of men, that the fates of mortals are various, and I cannot tell whether I should class myself in the number of the happy or of the miserable. When I contemplate my fate on the one side, I account myself most happy; but if on the other side, no one is more miserable." Balbinus urged him to make the matter as brief as possible. "I will have done immediately, most learned Balbinus," said he," and it will be the more easy for me in the presence of a man who

he referred to, he replied, "Good sir, you know (for what escapes Balbinus, a man of such erudition?) that there are two ways in this art: one, which is called *Longation*; and the other, which is called *Curtation*. Through my bad fate I have fallen upon *Longation*." When Balbinus asked him what was the difference between the ways, he replied, "It would be impudent in me to mention this to a man to whom, as I am very well aware, all things are so well known that nobody knows them better. Therefore I come as a suppliant before you, that you may take pity upon me, and deign to impart to me that most happy way of *Curtation*. And the fact that you are so expert in this art will make it a much simpler task to impart it to me. Do

not conceal so great a gift from your poor brother, who is ready to die with grief, and may Jesus Christ ever enrich you with more sublime endowments."

When he would make no end of his entreaties, Balbinus was obliged to confess that he was utterly ignorant of the whole matter of *Longation* and *Curtation*, and bade him explain the meaning of the terms. Then the priest began: "Although, sir, I am aware that I am speaking to a person better skilled than myself, yet since you command me, I will do as you wish. Those that have spent their whole lives in this divine art change the species of things in two ways: one shorter, but full of danger; the other longer, but safer. I count myself unhappy that I have learned in that way which is not adapted to my disposition; nor have I been able, up to this time, to find anybody who would show me that other way, which I am so desirous of learning. But at last God put it into my mind to apply to you, a man not less pious than learned. Your learning enables you to grant easily what I seek, and your piety will dispose you to help a Christian brother, whose salvation is in your hands."

To make the matter short, long before the old fox, with talk of this kind, had cleared himself of all suspicion of a trick, and had established the belief that he understood one way perfectly well, Balbinus' mind was itching with curiosity. At last, when he could hold out no longer, he cried, "Away with your methods of *Curtation*, of which I have never before heard even the name, so far am I from understanding it. Tell me, sincerely, do you thoroughly understand *Longation*?" "Pooh!" replied the priest, "perfectly well. But I don't like the tediousness of it." Then Balbinus asked him how much time it would require. "Too much," replied the priest, "almost a whole year; but in the meantime it is the safest way." "Never mind about that," said Balbinus, "if it should take two years, if only you can depend upon your art.

To shorten the story, they came to an agreement that the business should be set on foot secretly in Balbinus' house upon this condition; the priest was to find the art and Balbinus the money, and the profit was to be equally divided between them, although the impostor modestly offered that Balbinus should have the whole gain. They took an oath of secrecy after the manner of those who are initiated into the mystic rites, and money was paid down for the artist to buy pots, glasses, coal, and other necessary

things for furnishing the laboratory. This money our alchemist squandered agreeably upon harlots, dice, and drinking.

*Philecous*: That is one way, however, of changing the species of things.

*Lalus*: When Balbinus pressed him to take vigorously hold of the matter, he replied: "Don't you know that 'well begun is half done?' It is of the first importance to have the materials well prepared." At last he began to set up the furnace, and here again was need for more gold, to be used as a bait for future gold; for as fish are not caught without bait, so alchemists must put gold in before they can take gold out. In the meantime Balbinus was wholly absorbed in his computations, for he reckoned thus: If one ounce makes fifteen ounces, what will be the product of two thousand ounces? That was the sum he had made up his mind to spend.

When the alchemist had spent the money entrusted to him in two months' time, pretending to be wonderfully busy about the bellows and the coals, Balbinus inquired of him how the work was going on. At first he made no answer, but upon Balbinus' urging he at length replied: "As all important matters go, the greatest difficulty is to make a beginning." A mistake had been made in buying the coals; he had bought oak coals, and it was necessary to have fir or hazel. There was a hundred florins gone, nor did he on this account betake himself less eagerly to the dice. The money was given, and new coals were bought, and the business begun again with renewed zeal, just as in war soldiers, if anything happens in the way of disaster, make it up in bravery. When the laboratory had been kept hot for some months, and the golden fruit was expected, and there was not a grain of gold in the vessels (for the alchemist had squandered all that), another pretense was found: that the glasses they had been using were not rightly tempered. For just as a Mercury cannot be cut out of every log, even so gold cannot be made in every kind of glass; and the more money that was spent, the more unwilling was Balbinus to give it up.

*Philecous*: So it is with gamesters, as if it were not better to lose some than all.

*Lalus*: Very true. The alchemist swore he was never so deceived since he was born, but now that this error had been detected the rest was sure, and he hoped to make up that loss with large interest. The glasses were changed, and the laboratory refurnished for the

third time. Then the operator warned his patron that the work would go on more successfully if he would send a present of a few florins to the Virgin Mother who is worshiped by the dwellers on the coast, for the art was a holy one, and not likely to prosper without the favor of the saints. Balbinus liked this advice exceedingly, being a very pious man, who never let a day pass without performing some act of devotion. The alchemist set out, therefore, upon this pilgrimage, but spent the votive offering in a bawdy-house in the next town. Then he came back, and told Balbinus that he had great hopes the business would turn out according to their desires, since the Holy Virgin seemed so to favor his offerings.

When he had labored for a long time, and not one grain of gold appearing, Balbinus expostulated with him, he answered that nothing like this had ever happened to him in all his life, as often as he had practiced the art, nor could he imagine what was the matter. After they had studied over the matter a long time, it occurred to Balbinus that perhaps some day he had omitted hearing the mass, or saying his prayers, for he was certain that nothing would succeed if these were omitted. "You have hit the nail upon the head," replied the impostor; "I, too, wretch that I am, have been guilty of the same crime once or twice through forgetfulness, and once of late, rising from the table, after a long dinner, I forgot to repeat the Salutation of the Virgin." "Why, then," said Balbinus, "it is no wonder that a thing of this moment succeeds no better." The rascal undertook to perform twelve services for two that he had omitted, and to repay ten Salutations for the one.

When money every now and then failed this extravagant alchemist, and he could find no pretext for asking for more, he finally hit upon this scheme. He came home with the air of one terrified to death, and in a mournful tone cried out: "Alas, Balbinus! I am lost, totally lost! I am in danger of my life!" Balbinus was stupefied, and sought to learn the cause of the disaster. "The people of the court," replied the priest, "have gotten wind of what we are about, and I expect nothing else but to be carried to prison immediately." At this Balbinus turned pale in earnest, for you know it is a capital crime with us for any man to practice alchemy without permission of the prince. "Not," continued the priest, "that I fear death for myself. Would that were the worst thing that could happen! I fear something more cruel." Being asked what that might be, he replied: "I shall be dragged

off to some castle, and there forced to work all my days for those I have no mind to serve. Is there any death that would not be preferred to such a life?" The matter was carefully considered, and Balbinus, who was well versed in the art of rhetoric, examined every possibility if this mischief might not in some way be averted. "Can't you deny the crime?" he suggested. "Impossible," replied the priest. "The matter is known among the people of the court, and they have proof which cannot be set aside; nor is it possible to avert the result, for the law is clear."

When many things had been proposed, and nothing seemed to afford a certainty of relief, the alchemist, who was in need of ready money, said, "Balbinus, we waste our strength in vain counsels, when the matter demands an immediate remedy. Already I think I hear them coming to carry me away to my cruel fate." Finally, seeing that Balbinus did not catch the point, he added: "I am as much at a loss as you, nor do I see any way left, but to die like a man, unless you approve of what I am going to propose, which would be more profitable than honorable, were not necessity a stern master. You know that these men are hungry after money, wherefore they may the more easily be bribed to secrecy. Although it is indeed hard to give these rascals good money to throw away, but as the case now stands, I see no better way." Balbinus was of the same opinion, and counted out thirty gold pieces to secure their silence.

*Philecous*: You make Balbinus out to be wonderfully liberal.

*Lalus*: Nay, in an honest cause, you would sooner have gotten his teeth out of his head than his money. Well, the alchemist was provided for, who was in no danger but that of wanting money for his mistress.

*Philecous*: I wonder Balbinus had no suspicion all this while.

*Lalus*: This is the only thing he lacks shrewdness in; he is sharp enough at anything else. Now the furnace was put to work again with new money, but first a short prayer was made to the Virgin to prosper their undertaking. By this time a whole year had been spent, first with one obstacle, then with another, so that all the expense and labor were lost. In the meantime a most ridiculous thing occurred.

*Philecous*: What was that?

*Lalus*: The alchemist had an intrigue with the lady of a certain courtier. The husband, beginning to be jealous, began to watch for the man, and, finally, having been informed that the priest was in his wife's bed-chamber, he came home unexpected, and knocked at the door.

*Philecous*: What did he intend to do with him?

*Lalus*: What? Why, nothing very agreeable; either kill or mutilate him. When the husband, being short of patience, threatened to break down the door if his wife did not open it, they were in bodily fear within, and looked about for some means of escape. Circumstances suggesting nothing better, the alchemist pulled off his coat and threw himself out of a narrow window, not without both danger and injury to himself, and so got away. Such stories as these, you know, spread rapidly. It came to the ears of Balbinus, but the artist was not unprepared for this event.

*Philecous*: So he was caught at last.

*Lalus*: Nay, he got off better here than he did out of the bed-chamber. Hear the man's invention. Balbinus said not a word to him about the matter, but showed it in his gloomy countenance that he was no stranger to the talk of the town. The alchemist knew Balbinus to be a man of piety, and in some respects, I should almost say, superstitious. Such persons are very ready to forgive a suppliant, no matter how grave his offense. Therefore the priest purposely began a talk about the progress of their business, complaining that it had not been exactly successful, not such as it had formerly been, or as he had hoped it would be, adding that he wondered greatly what might be the reason. Upon this Balbinus, who hitherto had been sunk in silence, was readily moved. "It is not difficult to see," said he, "what the trouble is. Sins are the obstacles that stand in the way of our success, for pure works must be undertaken by pure persons."

At this word the trickster fell upon his knees, beating his breast, and with a countenance and voice full of tears cried: "O, Balbinus, what you have said is true indeed. It is sin indeed that hinders us, but my sin, not yours. I am not ashamed to confess my uncleanness before you, as I would before my most holy father confessor. The frailty of my flesh o'ercame me, and Satan drew me into his snares. Miserable wretch that I am; of a priest I am become an adulterer! And yet the offering which you sent to the Virgin Mother is not wholly lost, for I had certainly perished if she had

not helped me, for when the husband broke open the door, and the window was too little for me, in that moment of danger I bethought me of the blessed Virgin; I fell upon my knees and besought her, that if the gift had been acceptable to her, she should help me, and without delay I went to the window (for the necessity was great), and found it large enough for my escape.

*Philecous*: Did Balbinus believe this?

*Lalus*: Believe it? Yes, indeed, and forgave him, too, and admonished him religiously not to be ungrateful to the blessed Virgin. And more money was paid down upon his giving his promise that he would thenceforth carry on the business with purity.

*Philecous*: Well, what was the end of all this?

*Lalus*: The story is very long, but I will cut it short. When he had fooled his man long enough with such inventions, and wheedled him out of a considerable sum of money, a certain person happened to come along, who had known the rascal from a boy. He readily suspected that he was acting the same part with Balbinus that he had acted everywhere, and secretly admonished Balbinus, telling him what sort of a fellow he was harboring in his house, and advised him to get rid of the rascal as soon as possible, unless he had a mind to have him rifle his coffers sometime and then run away.

*Philecous*: Well, what did Balbinus do then? Surely he took care to have him committed to prison?

*Lalus*: To prison? Nay, he gave him money for his journey, conjuring him, by all that was sacred, not to speak of what had happened. And he was wise, in my opinion, to do this, rather than to become the subject of an after-dinner joke, and run the risk of having his goods confiscated besides. For the impostor was in no danger. He knew no more of his art than an ass, and cheating is the breath of life to people of that sort. If he had charged him with theft, his cloth would have kept him from hanging, and nobody would have been willing to maintain such a fellow in prison.

*Philecous*: I should pity Balbinus, but that he took pleasure in being swindled.

*Lalus*: I must make haste to the court. At another time I'll tell you stories more ridiculous than this.

*Philecous*: When you are at leisure, I shall be glad to hear them, and I will give you story for story.

# THOMAS MIDGLEY, JR., AND THE INVENTION OF CHLOROFLUOROCARBON REFRIGERANTS:  IT AIN'T NECESSARILY SO

Carmen J. Giunta, Le Moyne College

The 75th anniversary of the first public description of chlorofluorocarbon (CFC) refrigerants was observed in 2005.  A symposium at a national meeting of the American Chemical Society (ACS) on CFCs from invention to phase-out (1) and an article on their invention and inventor in the *Chemical Educator* (2) marked the occasion.  The story of CFCs—their obscure early days as laboratory curiosities, their commercial debut as refrigerants, their expansion into other applications, and the much later discovery of their deleterious effects on stratospheric ozone—is a fascinating one of science and society well worth telling.  That is not the purpose of this article, though.

This paper is about contradictory sources, foggy memories, the propagation of error, and other obstacles to writing accurate historical narratives.  It is about the digging, sifting, and weighing that historians do in order to piece together accounts that describe as accurately as possible a sequence of events, causes, and effects as they really happened.  Professional historians, no doubt, can write numerous similar articles based on the path of their own researches; they will find nothing noteworthy in this article unless they find Midgley and the invention of CFC refrigerants interesting.



*Thomas Midgley, Jr.*
*Courtesy Richard P. Scharchburg*
*Archives, Kettering University*

Critical readers are well aware of the importance of evaluating sources of information.  For example, an article in *Nature* at the end of 2005 tested the accuracy of two encyclopedias' entries on a sample of topics about science and history of science (3).  A thoughtful commentary published soon afterwards raised questions on just what should count as an error in assessing such articles: omissions? disagreements among generally reliable sources (4)?  Readers of historical narratives who are neither practicing historians nor scholarly amateurs (the category to which I aspire) may find an account of a historical research process attractive.  As a starting point, consider the following thumbnail summary of the invention.

Fatal accidents due to refrigeration leaks, including a disaster at a Cleveland hospital, placed refrigerants under the scrutiny of municipal health officials and the American Medical Association (AMA).  Frigidaire needed a nontoxic, nonflammable refrigerant, and Charles Kettering asked Thomas Midgley, Jr., to find one (5).  It didn't take Midgley and his associates Albert Henne and Robert

McNary long to focus on fluorine-containing compounds and to make dichlorofluoromethane ($CHCl_2F$) (6). Dichlorodifluoromethane ($CCl_2F_2$) was the compound that was eventually developed and announced as the first fluorinated refrigerant (7). The new refrigerant, dubbed Freon, took over the growing household refrigerant market during the 1930s, and closely related compounds were used widely in air conditioning.

Midgley was not a chemist by training, but a mechanical engineer, although the refrigerants were his second major chemical invention. He had led the team that discovered the knock-suppressing properties of tetraethyllead and developed leaded gasoline. Having contracted polio late in life, he applied his inventiveness to design a rope pulley or harness system that allowed him to move between his bed and wheelchair. An accident involving the system caused his death by strangulation in 1944 at the age of 55 (8).

These two brief paragraphs are not drawn from any single account, but some combination of these or similar statements can be found in popular and scholarly treatments of the subject in books, periodicals, and web pages. They contain several statements that are at least debatably if not demonstrably inaccurate. A series of fatalities related to refrigerant leaks in 1929 did receive national publicity and the scrutiny of the American Medical Association; however, Midgley and associates had already made and begun to test fluorinated refrigerants in 1928. A horrific fire and explosion causing over 100 fatalities, many of them from poisonous gases, did indeed strike the Cleveland Clinic in 1929; however, refrigerants were not involved. $CCl_2F_2$ was certainly the first fluorinated compound announced, developed, and manufactured as a refrigerant, but whether it or $CHCl_2F$ was the first compound made and tested for that purpose is unclear. Midgley was indeed a mechanical engineer by training, who became one of the most celebrated industrial chemists of his time. His associates publicly described his death in 1944 as an accident; however, contemporary death records and some private comments by associates assert that it was a case of suicide. Even the authorship of the obituary cited above is questionable: one of Midgley's colleagues, Thomas Boyd, wrote that he prepared several obituaries of Midgley published under the name of another associate, Kettering.

Clarifying the record on these points where possible is one purpose of this article; its other purpose, as already stated, is to describe the difficulties of unraveling a complicated story.

## What Prompted the Search for Safe Refrigerants?

The erroneous assumption that highly publicized fatalities involving leaks of household refrigerants in 1929 prompted the invention of nontoxic, nonflammable refrigerants announced in 1930 is a combination of a mistaken chronology and the logical fallacy *post quam ergo propter quam* (literally "after it, therefore because of it"). To assume that the headlines about refrigerants in 1929 and 1930, detailed below, served as a spur to industry may be understandable, but it is not correct.

A cluster of deaths in Chicago in mid-1929 drew attention to the dangers of refrigerant leaks. In early July, a coroner's jury of pathologists and chemists found (9):

> At least fifteen and perhaps more persons died in recent months in Chicago from gases used in artificial refrigeration. ... Four persons have been victims of the gas [methyl chloride] in the last ten days in Chicago. Dr. Kegel [Health Commissioner] compiled a list of twelve persons who, he said, had been made ill by the gas, and a list of seven who had died from it in the last few weeks.

After the death of a couple and their one-year-old son two weeks later, Kegel ordered a local ban on the use of methyl chloride as a refrigerant. The Peerless Company, which manufactured the refrigerator, immediately announced that his company would stop making methyl chloride refrigerators until the cause of the deaths was determined (10).

The Chicago incidents were reported in newspapers across the country, albeit in relatively small stories on inside pages. Governmental, professional, and industrial groups were also taking notice. The US Public Health Service, Bureau of Standards, and Bureau of Mines issued a joint statement on July 31 intended to prevent "undue excitement." The statement explained basic principles of household refrigeration, and it explained that the three most important refrigerants in such machines were ammonia, sulfur dioxide, and methyl chloride (11):

> None of the three refrigerants ... can be breathed with impunity, but none are violent poisons when breathed for a short time in low concentrations.

It explained, correctly, that methyl chloride is the least poisonous; however, the others are so malodorous and irritating that "no one is likely to breathe much of them if escape is possible." The Bureau of Mines had recently investigated exposure to methyl and ethyl bromide and chloride in research pursued under a cooperative agree-

ment with Dow Chemical Company.  The idea behind this investigation was to mix the more toxic but fire-retarding bromides with the less toxic but more flammable chlorides to produce a refrigerant safe for homes, public buildings, and mines (12).  The Bureau of Mines also explored the idea of introducing an odorant into methyl chloride to act as a warning agent (13).

Dr. Morris Fishbein, editor of the *Journal of the American Medical Association*, had headed the Chicago panel mentioned above.  Later in the summer of 1929, the AMA appointed a committee to look into methyl chloride in domestic refrigeration (14).  In 1930 the AMA Committee on Poisonous Gases published a report on household refrigeration.  The report dwelt on methyl chloride at some length, rating it the most dangerous of six refrigerants for delayed toxic effects.  Ammonia and sulfur dioxide were rated worst for immediate toxic effects.  Warning agents might reduce the dangers associated with methyl chloride, but the report did not endorse adding toxic odorants to toxic refrigerants; in any event, warning agents can help only those who can escape, not infants or the physically or mentally disabled (15).

Manufacturers and advocates of methyl chloride as a refrigerant thought it was being unfairly criticized, and they maintained that it was safe when used properly.  They emphasized the fact that when serious methyl chloride poisoning occurred, a central compressor employed to cool refrigeration units in multiple apartments leaked its large charge of refrigerant into the relatively confined space of one of those apartments.  (Indeed, the government bureaus' statement and the AMA report also faulted large central refrigerators for their potential to deliver a large charge of harmful material.)  During the next year, though, the AMA and advocates of methyl chloride traded polemics in their respective professional and trade journals (16).

A link between methyl chloride and a terrible explosion and fire at a Cleveland hospital, erroneously asserted in some accounts of the invention of CFCs, seems to be an odd artifact of AMA involvement in the methyl chloride controversy.  As far as I have been able to determine, the link between methyl chloride and the Cleveland Clinic disaster was first made in 1954, in Williams Haynes' *American Chemical Industry* (17):

> A disastrous accident in a hospital in Cleveland gave methyl chloride a severe setback, and the American Medical Association went out of its way to wage war against it.

In May 1929, an explosion and fire at the Cleveland Clinic killed over 120 people, and most of the deaths were in fact due to breathing poisonous gases.  The gases, however, were carbon monoxide and a mixture of nitrogen oxides formed from the burning of highly flammable nitrocellulose X-ray film—not methyl chloride.  The explosion was traced to an unventilated storage room that housed X-ray film.  On the day of the disaster, a leak had been detected in one of the high-pressure steam lines that ran through the room.  Repairs were undertaken, insulation removed, and the steam line shut off, but not, apparently, before some decomposition of nitrocellulose began to trigger the disaster (18).

Naturally, this appalling tragedy was widely reported, investigated, and discussed.  Initial reports included descriptions of people overcome by fumes (19) and comparisons to chemical warfare agents (20).  Nitrogen oxides and carbon monoxide were soon identified as the compounds mainly responsible for the deaths and injuries caused by inhalation (21).  A report released about a month later by a military panel working under Major General Harry Gilchrist, Chief of the Chemical Warfare Service, supported these conclusions.  Gilchrist had arranged for tests involving the ignition of large quantities of nitrocellulose X-ray film at a Chemical Warfare Service facility.  As the report pointed out, the armed forces had some experience with burning and igniting nitrocellulose (22).

I found no reference to methyl chloride in contemporary reporting on the Cleveland disaster, including reports of investigations, and I found no mention of the Cleveland accident in connection with the debate on the safety of methyl chloride in 1929 or the early 1930s.  More telling than this negative evidence is an August 1929 editorial in the *Journal of the American Medical Association* that discussed the Cleveland Clinic disaster and the spate of methyl chloride poisonings in Chicago as two separate examples of dangers due to poisonous gases (23).  It is clear, then, that no well informed sources at the time had any reason to believe that methyl chloride was implicated in any way in the Cleveland Clinic accident.

How Williams Haynes came to connect methyl chloride to the Cleveland Clinic fire decades later is not clear—if he was indeed the first to have forged the erroneous link.  The relevant statement appeared in a section of *American Chemical Industry* that discussed refrigerating chemicals.  None of the references provided in that section suggests any such connection. Perhaps Haynes saw and conflated or confused the two instances of hazardous

gases in the AMA editorial; this is plausible, given that he mentioned the AMA in connection with methyl chloride and the Cleveland Clinic.

*American Chemical Industry* is a well researched and authoritative multi-volume reference work.  It is a plausible but by no means definite source for the propagation of this phantom connection in later books and articles.  *Science and Corporate Strategy: Du Pont R&D, 1902-1980* (24) and *Between Earth and Sky: How CFCs Changed Our World and Endangered the Ozone Layer* (25) are later well documented volumes that also blame methyl chloride for the Cleveland Clinic disaster. In both of these books, the only reference given for the statement is to a 1929 *New York Times* report that does not mention methyl chloride (Ref. 19 in this paper); however, *American Chemical Industry* is in the general bibliography of both.  Both have been cited in still later publications as the source for similar statements.

Even without the Cleveland Clinic disaster, the string of fatal refrigeration accidents in Chicago and the publicity they generated around the deficiencies of household refrigerants make for a plausible motivation for seeking new and safer refrigerants.  The accidents, however, took place after the research that some sources say they inspired.

The first public announcement of the invention of CFC refrigerants took place in April 1930 in Atlanta at the 79th national meeting of ACS.  It focused on the properties of $CCl_2F_2$; it did not include an account of the circumstances that led to the invention.  A paper based on the conference presentation also appeared in 1930 (7). The patent application for CFC refrigerants was also filed in that year (26).  1930 is certainly the public birthday of CFC refrigerants.

The year of the actual invention, though, was 1928 according to archival sources and published accounts that cite such sources.  Scholarly papers by Stuart Leslie (27) and Mohinder Bhatti (28) cite oral history interviews and correspondence involving several individuals in their accounts of the invention of CFC refrigerants.  Most of these materials can be found in the Charles F. Kettering Collection in the Richard P. Scharchburg Archives at Kettering University (formerly the Alumni Foundation Collection of Industrial History at the General Motors Institute).  I have also seen reports put together on the history of Frigidaire that set the date of the invention as 1928 (29).  These archival materials generally date from the mid-1940s to mid-1960s.  They are not, therefore, as definitive as dated laboratory notebooks, for example;

however, they constitute a number of independent recollections that converge on the same date.

The Chicago methyl chloride accidents could not have been the spur to the invention of CFC refrigerants, then.  To assume that an earlier event is the cause of a later one is dangerous—particularly if the purportedly later event actually preceded its putative cause!  Assumptions can be dangerous even when the chronology is more or less correct.  A fictionalized account of the invention of CFC refrigerants has one of its characters castigate Midgley's company for making and selling dangerous refrigerators even after discovering a safe refrigerant (30):

> Do you mean to say you know how to make a non-poisonous refrigerant, but you're still manufacturing new refrigerators that use methyl chloride, the same gas that poisoned all those people up in Cleveland last month?

While avoiding the error of asserting that methyl chloride leaks inspired the invention of CFC refrigerants, the question fails to recognize the time it takes to develop a practical product after discovery, time for testing and time to devise and build manufacturing facilities.  (By the way, the refrigerator manufacturer connected to Midgley's research efforts, Frigidaire, actually made refrigerators that operated on sulfur dioxide, not methyl chloride.)

If dramatic refrigeration accidents were not the spur to invention, what was?  Several other explanations have been offered, but there is no clear answer. The same sources that place the date of the invention in 1928 agree that in that year Charles Kettering, head of General Motors Research, asked Midgley to develop a safe refrigerant.  Nonflammability and nontoxicity were two of the principal criteria.

The way Midgley recalled it, nearly a decade afterwards, was that Kettering and associates at Frigidaire (which was owned by General Motors) "came to the conclusion that the [household] refrigeration industry needs a new refrigerant if they ever expect to get anywhere." (6)  Thomas A. Boyd, another GM research associate of Midgley and Kettering, said that a safe refrigerant would be necessary before air conditioning could take off (31).  The subsequent development of automotive air conditioning in the 1930s also looks like a plausible incentive for a refrigeration concern owned by an auto company.

None of these reasons withstands critical examination as a sole or primary motivation, however.  The 1920s

were growth years for household refrigeration in general, Frigidaire included.  Industry-wide sales increased from about 65,000 refrigerators in 1925 to 730,000 in 1929 without new refrigerants (24).  Frigidaire had survived its beginnings as the undercapitalized Guardian Frigerator Company in 1916-18 and its subsequent overextension under General Motors in the early 1920s.  After its move from Detroit to Dayton under the umbrella of the Delco-Light subsidiary of GM, Frigidaire turned around.  It introduced a less bulky air-cooled machine in 1924, and by January 1928, it regained independence from Delco-Light.  The millionth Frigidaire refrigerator came off the production line in 1929.  That same year, Frigidaire introduced its first room cooler (29b).  During this time of growth, Frigidaire used sulfur dioxide refrigerant.

The question of why Kettering put Midgley on the project of developing safe refrigerants when he did was one that Frigidaire chronicler Thomas Shellworth asked but did not have answered.  Shellworth worked in the public relations department of Frigidaire when he wrote a history of the company during the late 1940s (29a).  Kettering was one of the people he interviewed as part of the project, and he asked Kettering why a search for safe refrigerants was initiated at that time.  According to Shellworth's notes, Kettering did not seem to like the question.  Indeed, those notes suggest an uncomfortable interviewer and a rather impatient interviewee, not surprising, perhaps, in light of Kettering's high position as a Vice President of the corporate parent (General Motors) of Shellworth's employer (32).

A later in-house chronicler of Frigidaire, Daniel Mc-Coy, suggested a less dramatic reason for the refrigerant research program.  Frigidaire wanted to expand in household refrigeration, air conditioning, and supermarket refrigeration.  For all the growth in the household sector during the late 1920s, a large majority of houses that had electricity still had iceboxes rather than refrigeration machines.  Air conditioning was in its infancy, so it had great potential for growth.  Frigidaire was also working on commercial projects, such as ice cream cabinets.  When Clarence Birdseye test-marketed frozen foods in 1930, Frigidaire provided the display cases (29b).  What these areas had in common was that they involved refrigeration machinery operated in the proximity of the general public.  This was in contrast to industrial refrigeration in workplaces like breweries and meat packers where the machinery was run by trained operators in the presence of a restricted population of workers.  Frigidaire entered these fields with sulfur dioxide machines, but a less noxious refrigerant would clearly have been more desirable.

In automotive air conditioning, the proximity of the machinery to the motor vehicle operator was even greater, as was the possibility of accidental discharge of the working fluid.  The GM Research Laboratories certainly took advantage of their invention of safe refrigerants to develop a vapor compression automotive air-conditioning system using $CCl_2F_2$ as the working fluid.  The idea surfaced in 1930, with a formal proposal following in 1932, and work beginning in 1933 (33).

Inferring causes for actions from incomplete or contradictory sources is part of the job of reconstructing events and telling their story.  Identifying a single or primary reason for action makes for a satisfying tale, but there does not seem to be any such dramatic trigger for the development of a safe refrigerant.  The deficiencies of existing refrigerants were generally known in the industry, although the extent of the danger was made dramatically apparent by the Chicago accidents of 1929.  The refrigeration industry was already expanding into areas that brought it into closer contact with the general public, and it was growing even with the old refrigerants.  Development of safe refrigerants seems to have been desirable, but not necessary.  GM decided to invest in such development in 1928, and it paid off.

## What was the First Fluorinated Compound Studied for Refrigeration?

There is no doubt that dichlorodifluoromethane $(CCl_2F_2)$ was the first fluorinated refrigerant developed for commercial use.  Whether or not it was the first compound made for the purpose of investigating possible fluorinated refrigerants is less clear.  As mentioned above, the announcement of the invention of fluorinated refrigerants focused on the properties of $CCl_2F_2$, the compound the researchers had decided to develop.  That announcement was not an account of the research process, and it was silent on whether or not other compounds had been examined in the course of the project (7).

Midgley gave a brief account of the discovery during his address on the occasion of being awarded the Perkin medal in 1937.  He described some of the reasoning that led him and his associates to turn their attention to fluorinated compounds.  The boiling point listed in the *International Critical Tables* for carbon tetrafluoride $(CF_4)$ would make it a promising refrigerant candidate; however, that published data point did not seem to be

consistent with those of the few other halomethanes listed. In his speech, as published in *Industrial and Engineering Chemistry*, he said, "We selected dichloromonofluoromethane [$CHCl_2F$] as the starting point for experimentation." (6) Albert Henne, Midgley's assistant at the time of the invention, later told interviewers that the first target compound was, in fact, the one that was eventually developed and marketed, $CCl_2F_2$ (20b, 34).

How does one choose between these statements, made by two principals of the invention? I first looked for corroboration for either statement, but found no other independent statements on the subject. Next I examined the statements for the possibility of a misprint or mis-statement. R. E. Banks and John Tatlow noted Midgley's mention of dichloromonofluoromethane in the Perkin Medal speech, but wrote that his previous and subsequent papers on the subject mention only dichlorodifluoromethane. They suspect that an "unfortunate printing error crept into this account." (35) I would consider it easy for a printer or transcriber to drop a prefix, turning dichlorodifluoromethane into dichlorofluoromethane; however, it would be much more difficult to inadvertently transform a "di" prefix to "mono," and the text says dichloro*mono*fluoromethane. (Is it possible to imagine, though, dropping a subscript in a chemical formula, turning $CCl_2F_2$ to $CCl_2F$, and having a transcriber unaware of the tetravalence of carbon write out dichloromonofluoromethane?) It is equally difficult to see any possibility of misunderstanding Henne's statements. Boyd asked him specifically, "The first compound you made, did it have any hydrogen in it or was it strictly carbon, chlorine, and fluorine?" McCoy wrote that when he interviewed Henne, the latter pointed out the error in the Perkin Medal address.

Knowledge of the chemistry involved does not help decide the question either. The reaction used to make fluorinated hydrocarbons was substitution for chlorine atoms by fluorine atoms from $SbF_3$ in the presence of a catalyst, a method pioneered by Frédéric Swarts. Carrying out the Swarts reaction on chloroform would produce $CHCl_2F$ (Swarts had done this himself) (36) and possibly also $CHClF_2$, depending on conditions. Carrying out the same reaction on carbon tetrachloride would produce a mixture of $CCl_2F_2$ and $CCl_3F$. Both possible chlorinated starting materials were readily available at the time.

Weighing fragmentary and contradictory evidence is part of the task of the historical researcher. In my judgment, Henne's accounts are more likely to be correct than Midgley's, mainly because Henne was the person who made these compounds. Henne was a Ph.D. chemist by training, and his dissertation work focused on halogenated derivatives of ethylene. He was the member of the research group who knew of the Swarts reaction. In addition, Henne's comments have the tone of someone speaking for the historical record, and his statements to two different researchers on this point were consistent. Midgley's comments appear to me to have been more casual. Others may legitimately come to a different conclusion by weighing the statements differently. After all, Henne's recollections were recorded only after the passage of decades while Midgley's were less than ten years old. In addition, Henne's interview with Boyd suggests that he was mistaken about the dates of the research: he invoked the Depression, which had not yet started at the time the refrigerant research began.

## Midgley's Death: Accident or Suicide?

Midgley could neither corroborate nor contest Henne's memory, for he had been dead nearly 20 years at the time of Henne's statements. Obituaries and early biographical sketches of Midgley described his death as a tragic accident that prematurely ended the life of a prolific inventor and public-spirited citizen. Undoubtedly his death was premature and tragic: he was only 55 when he died, an invalid because of polio contracted after the age of 50. He was strangled by a harness he had devised to allow him to move between bed and wheelchair. At the time of his death in 1944, his two best known inventions, leaded gasoline and CFC refrigerants, were used widely with no hint of the environmental problems that would later become apparent (37). Some considered Midgley to be a public benefactor because of these inventions; in any event, his service on a wartime inventors' council, on the ACS board, and elsewhere displayed a civic orientation.

Some knew or suspected that Midgley's death was no accident even at the time. The death certificate signed on the date of his death lists the cause of death as suicide by strangulation. Henne, called to the scene by the newly widowed Carrie Midgley, confided to a colleague, "That was no accident." (38) Suicide carried a considerable stigma in 1944, arguably a much greater one than at present. It cannot be surprising, then, that close colleagues and family members did not speak of suicide in public, whether because of concern for Midgley's reputation or because they did not know or believe that it was a suicide. Thomas Midgley IV, for example, does not mention suicide in his biography of his grandfather (39).

Boyd was one of those colleagues who wrote quite a bit about Midgley in several different contexts, and there is no suggestion in these writings that Midgley's death was suicide.  The most public of Boyd's writing about Midgley was a belated obituary published in the *Journal of the American Chemical Society* in 1953.  In that piece, Boyd calls Midgley's death "unexpected." (31)  In an unpublished typescript autobiography, Boyd recalls that Midgley concluded his ACS Presidential address "Accent on Youth" at the September 1944 ACS meeting with the following lines from a poem he had written,

> Let this epitaph be graven on my tomb in simple style,
>
> "This one did a lot of living in a mighty little while."

Boyd went on (40):

> Whether that ending had any significance as a portent of the future, I don't know.  But less than two months later, on November 2, 1944, Midgley died.

On the question of suicide, Boyd is silent, whether writing explicitly for publication (41) or not (42).

The mention of suicide entered published works about Midgley only decades after his death (43).  But now that the environmental side effects of his best known inventions are widely recognized, the story of accidental strangulation persists and provides a final irony in many short versions of the tale of Thomas Midgley, Jr.  Several internet pages on Midgley take up the theme of unintended consequences, of double-edged inventions.  Leaded gasoline and CFCs are examples writ large, and the harness that strangled its inventor is a personal example (44).  Sometimes the irony is more heavy-handed than others.  Joe Schwarcz, Professor of chemistry at McGill University, writes of seeing a play in which Midgley's death was characterized as a just reward for his harmful inventions (45).

I have no evidence that any of the sources mentioned here mischaracterized Midgley's death as accidental in deliberate contradiction of the facts.  Certainly some at least did not know or believe that it was a suicide.  Nonetheless, the accident story fits well with the overarching narratives of some, whether those narratives were admiring tributes to Midgley or cautionary tales of unintended consequences.

## Conclusion

How ought one to rewrite the thumbnail summary of the invention of CFCs with which this paper began?  One answer is to replace it with the content of this article from that point to this.  Detailed accounts, replete with documentation from contemporary and archival sources, are the scholarly products of historical research.  Such accounts are the means by which historical researchers communicate with each other and with other experts such as teachers or with the most interested and competent of lay readers.  Such accounts are not, however, suitable for less expert or less interested readers.  More condensed accounts are required in such publications as encyclopedias, textbooks, general interest magazines of history (or science or technology), and books with a broader historical or scientific scope.

Getting the facts correct would seem to be an uncontroversial prerequisite for writing history, whether for a scholarly or a general audience.  Without factual accuracy, judgments and interpretations will be suspect; and even factual accuracy does not guarantee correct interpretation.  What is one to do when the facts are complicated or uncertain?  Many writers for a general audience are not expert historical researchers.  They have little choice but to rely on the most reliable products of such researchers, distilling and condensing as appropriate.

Historical researchers writing for a general audience at least should know where the complications and uncertainties lie.  Even so, avoiding oversimplification is not easy.  In some cases, it may be preferable to omit a complex or uncertain point rather than to oversimplify it.  After all, recognizing the important and leaving out the nonessential is a necessary skill in writing abridged accounts for a popular audience.  For example, I would omit any reference to the Cleveland Clinic in an abridged account of the invention of CFCs; the tale of how it came to be erroneously associated with refrigerants is an interesting back story for aficionados of history, but not a part of the story of refrigeration.  Another strategy is to avoid the language of cause and effect where such language is not appropriate, choosing instead to describe features of the milieu in which an event occurred.  For example, fatal refrigerant leaks and the use of toxic refrigerants were features of the time during which CFC refrigerants were developed, even if they were not significant drags on the growth of household refrigeration or direct inspiration for the invention of CFC refrigerants.

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25.   S. Cagin and P. Dray, *Between Earth and Sky:  How CFCs Changed Our World and Endangered the Ozone Layer*, Pantheon Books, New York, 1993.  The Cleveland Clinic disaster is mentioned on p 61.  This book is the best researched and most complete account of CFCs from invention to scheduled phase out currently available.  The Cleveland Clinic disaster represents one of remarkably few factual errors.  In my opinion, the book's main shortcoming is a somewhat shaky scientific perspective.  It fails to explain, for example, that sound reasons for skepticism of Sherwood Rowland's and Mario Molina's 1974 proposal that CFCs harmed the ozone layer co-existed with the better described stupidity and greed that also beset the proposal.

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36.  F. Swarts, "Étude sur le fluochloroforme," *Bulletins de l'Académie royale des sciences, des lettres et des beaux-arts de Belgique*, **1892**, *24*, 474-484.

37.  Some readers who know that the introduction of leaded gasoline was controversial may take exception to the statement that it was not regarded as harmful in 1944. Concerns about lead emitted by automobile exhaust were raised by public health officials in the 1920s, and sales of leaded gasoline were suspended shortly after they began, pending investigation.  These concerns ultimately proved to be well founded.  Leaded gasoline was not shown to be harmful at the time, though, and at the time of Midgley's death it was in widespread use and under no cloud.

38.  Quoted in Cagin and Dray, Ref. 25, p 375.

39.  T. Midgley IV, *From Periodic Table to Production: The Biography of Thomas Midgley, Jr.* Stargazer Publishers, Corona, CA, 2001.  This book is amateurish in both laudatory and pejorative senses.  Clearly the author has affection for his subject, and he includes important archival material.  At the same time, the book depends slavishly on some of its sources and displays little or no critical judgment.

40.  T. A. Boyd, "Looking Back at My Life after 30" (1966 typescript); Thomas Alvin Boyd papers, 1921-1982, Ohio State University Rare Books and Manuscripts Library.

41.  In his typescript autobiographical memoir, Boyd states that he had prepared several pieces about Midgley for Kettering that were published under Kettering's name. These include "A Tribute to Thomas Midgley, Jr.," *Ind. Eng. Chem.*, **1944**, *36*, 1179-1182; "Thomas Midgley, Jr., An Appreciation," *Science*, **1944**, *100*, 562-564; and Midgley's biographical memoir for the National Academy of Sciences (Ref. 8).

42.  It is worth noting that although Boyd's autobiographical typescript was not for publication, it is likely that he was writing in some sense "for the record."  Boyd had already worked on oral history projects on both sides of the microphone.  He had interviewed many associates of Charles Kettering (See Ref. 34).  He had also been interviewed by Joseph Ermenc of Dartmouth College about the discovery of tetraethyllead as an antiknock agent.  Ermenc would also interview Boyd in 1966 about his recollections of Midgley.  Transcripts of Ermenc's interviews of Boyd are included among the Thomas Alvin Boyd papers, 1921-1982, Ohio State University Rare Books and Manuscripts Library.

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44.  Kauffman's article (Ref. 2) contains many references to internet pages about Midgley of highly variable quality; most of them adopt the unintended consequences theme. Kauffman also makes perceptive comments about the description of Midgley's death over the years as accident, then suicide.

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# CHEMISTS AND NATIONAL EMERGENCY: NIH'S UNIT OF CHEMOTHERAPY DURING WORLD WAR II.

Leo B. Slater, Office of NIH History and Museum

In 2005, President George W. Bush came to the National Institutes of Health (NIH) in Bethesda, Maryland, to announce a new initiative on avian and pandemic influenza (1). This visit was part of a long tradition. In the face of national emergencies and threats to public health, the NIH has repeatedly been called upon to serve the nation. In the years leading to US entry into World War II, the NIH mobilized to confront the impending threat of malaria. In the late 1930s, malaria was in sharp decline in the US. However, war would put millions of previously unexposed soldiers, sailors, and marines into highly malarious regions, such as the Mediterranean, South East Asia, and the islands of the Pacific. Even at home, many military bases would draw inductees to areas of the South and West where mosquito vectors could readily spread the debilitating and potentially deadly disease in crowded camp conditions. NIH researchers had to prepare anew for war and disease.

In 1938, Surgeon General of the US Public Health Service (USPHS) Thomas Parran and Rolla E. Dyer, chief of the Infectious Diseases Division at NIH, planned the transfer of two drug discovery groups from the University of Virginia and the University of Michigan to NIH in Bethesda. Heading the Virginia unit was Lyndon F. Small, who had trained in chemistry with Elmer P. Kohler and James B. Conant at Harvard and with Heinrich Wieland in Munich (2). With the intention of controlling drug addiction by altering the chemistry of opiates, Small's university program had synthesized novel compounds and modified existing ones in order to explore the chemistry and activity of morphine-related substances. The Michigan unit, which tested Small's compounds, was headed by Nathan B. Eddy, a Cornell-trained physician and pharmacologist. Parran, who had been Surgeon General since 1936, brought the two to Bethesda not to pursue analgesics, but to form the core of a new antimalarial chemotherapy laboratory (3). In January, 1939 Small and Eddy formed the nucleus of a new Unit of Chemotherapy at NIH. Both men were affiliated with the USPHS—a necessity if they were to handle narcotics—as part of their opiate work, which was funded by the Rockefeller Foundation and sponsored by the National Research Council (NRC). Their transfer to Bethesda was logical in the context of their NRC and USPHS connections.

Like many in the Federal government, Parran foresaw US involvement in World War II and knew that this would put many Americans at risk for malaria around the world. Parran's initiative became part of a larger project on antimalarial chemotherapy begun by NRC in 1939 (4). At the time only a handful of drugs was available for malaria treatment and prophylaxis. As NRC put it (5):

> While quinine, plasmoquine, atabrine and a few other drugs have been quite useful, there is, in the judgment of the medical profession, a great need for something better.

The need was great for a number of reasons. Ninety percent of the world's quinine originated on the island of Java in the Netherlands East Indies, an area under threat from Japanese military expansion in Asia. Plasmoquine

and atebrine were relatively new synthetic products developed and owned by the German chemical firm Bayer. All three of these major drugs had toxicity problems. To respond to the military need for better drugs, Small had to move his people to Maryland and quickly convert his chemotherapy program from opiates to antimalarials.

With war looming, Lyndon Small established a first-rate chemical group at NIH. He brought with him from Virginia the Vienna-trained chemist Erich Mosettig. Small also recruited to NIH Everette L. May, who earned his Ph. D. at Virginia in 1939. May and Mosettig began their antimalarial efforts with materials taken directly from the opiate research program. The new antimalarial program was collecting interesting compounds from laboratories around the country for random screening. Many chemists in academic, industrial, and government laboratories contributed samples for screening in the national antimalarial program. While no one thought these opiate-related materials were necessarily promising as antimalarials, the wartime project was soliciting all potentially biologically active compounds for their large-scale screening program. Also, Small had previously sought to replace the naturally occurring alkaloid morphine with a synthetic analogue, so it made some sense to follow a similar path in looking to replace another naturally occurring alkaloid, quinine. Therefore, May and Mosettig submitted to animal testing a number of amino alcohol derivatives of phenanthrene, which they had synthesized in their opiate work. They also synthesized a series of compounds based on quinine, what they called "quinuclidine with two C-C bonds disrupted." (6) Much of May's wartime work involved various derivatives of phenanthrene. NIH chemists also synthesized other chemical series for testing. For example, when one of Eddy's S-glucosides—phenyl-β–D-glucothioside (SN-5,859)—showed slight activity against the chicken-malaria screen (*Plasmodium gallinaceum*) and relatively low toxicity in chicks, Edna M. Montgomery, Nelson K. Richtmyer, and C. S. Hudson submitted nearly forty sulfur-containing compounds of various structural types (7). Small's NIH group also included other organic chemists, such as Lewis J. Sargent, who had been a National Research Fellow at Virginia in 1938-1939. He and Small worked on the acridines, a series of compounds related to the prewar synthetic antimalarial atebrine and on developing sulfanilamide derivatives as antimalarials (8). Various sulfas, such as Parke-Davis's Promin, had shown some promise as antimalarials even before the war.

For screening compounds, Small brought G. Robert Coatney from the NIH laboratory in Columbia, South

Carolina. The Columbia laboratory had been founded in 1931 by Louis L. Williams, Jr., of NIH's Office of Malaria Investigations. He and Bruce Mayne—another eminent NIH malariologist—had sought to establish a laboratory to refine the use of malaria in the treatment of neurosyphilis and to study the biology of malaria. It was Mayne who selected the South Carolina State Hospital as the laboratory's location and served as its first chief until his death in 1941. At Columbia, Coatney learned firsthand about the use of malaria to treat syphilis: how to employ this therapeutic intervention in one disease in order to study another. The use of malaria therapy—wherein malaria's high fever spikes were believed to benefit neurosyphilitics—was first developed in Europe in the 1910s and had expanded in the US during the 1930s (9). Coatney, trained as a protozoologist, had come from Nebraska in 1938 and joined the Columbia staff to develop for research purposes a pigeon malaria he had previously isolated. With the Columbia experience behind him, Coatney was able to establish avian malarias—particularly the chicken malaria *Plasmodium gallinaceum*—for the screening of potential drugs at NIH's animal facilities in Beltsville, Maryland (10). Coatney would also develop NIH's antimalarial clinical testing programs, first at St. Elizabeths Hospital in the District of Columbia and then, in 1944, at the Federal Penitentiary in Atlanta, Georgia (11). By 1941, even before Pearl Harbor, the efforts made by NRC and Parran had been significantly augmented by the new Federal Office of Scientific Research and Development (OSRD) and its Committee on Medical Research (CMR) established by President Franklin D. Roosevelt. Before the advent of OSRD, Small ran the only comprehensive antimalarial synthesis program in the country. As a part of this much larger CMR program, Coatney and Small expanded clinical testing efforts at NIH. At St. Elizabeths, Coatney's collaborators tested antimalarial compounds in neurosyphilis patients undergoing malaria therapy. The induced malarial fever had a therapeutic effect on these patients, and the drug interventions could be made after the fever had run its course over a suitable interval. In Atlanta, the research was conducted with prisoner volunteers, again with malaria induced either by the injection of infected blood or by the bite of infected mosquitoes raised for this purpose. These programs tested potential drugs produced not just in Small's laboratory, but by other collaborators in OSRD's expanding antimalarial program.

The wartime antimalarial program was a large-scale cooperative project, spread across scores of laboratories in government, academe, industry, and nonprofit orga-

nizations. So it is not surprising to find that the NIH worked with industrial collaborators, such as G. Carsch, Melvin A. Goldberg, E. P. Ordas, and J. Schultz from Lady Esther, Ltd., of Chicago, who expanded the phenanthrene series in new directions. After the war, these industrial chemists pursued careers at a number of firms including Velsicol Corporation, Lever Brothers Company, and New York Quinine and Chemical Works, which was one of Small's industrial collaborators on his opiate work (12). Additional academic collaborators, funded with OSRD money, were also essential to the work. Key compounds in the phenanthrene series were scaled up for testing by Ralph L. Shriner and his group at Indiana University and Charles C. Price's team at the University of Illinois.

During the war, several amino alcohol derivatives of phenanthrene showed activity similar to that of quinine, but often with some toxic effects. The phenanthrene series did eventually have one postwar chemical cousin with some clinical success, halofantrine, which emerged from clinical trials in the late 1980s. It retained the amino alcohol moiety but added a more modern trifluoromethyl substituent to the ring system (13). In the fall of 1944, however, adverse reactions in this series led Small and Mosettig to the conclusion (14):

> ..that the phenanthrene series appeared to be exhausted with the exception of the lot of drudgery to be done in the hope that some derivative other than those already under examination would turn up with a higher antimalarial activity.

The compounds had mostly been tested in human subjects at Alf Alving's University of Chicago program, which employed prisoner volunteers at the state prison in Joliet. None of these compounds showed sufficient antimalarial activity at the time to justify further pursuit (15), so they were dropped from the program. After the war with the need for secrecy over, the NIH laboratory



*James A. Shannon*

and its collaborators published dozens of papers on their work, including more than 20 in a series entitled "Attempts to Find New Antimalarials," which appeared in the *Journal of Organic Chemistry* in 1946 and 1947. In the postwar years, the NIH chemists and their government colleagues for the most part returned to their prewar pursuits. Small and Eddy resumed their work on analgesics, while Coatney and his colleagues, malariologists before the war, continued in this field.

The CMR antimalarial program, of which Small's group was a part, did much more than successfully reappraise chloroquine, the postwar antimalarial of choice. It developed safe and effective protocols for the use of atebrine during the war and tested more than 14,000 compounds for antimalarial activity, many of which were new substances synthesized expressly for the program. Some 80 compounds—including a number of NIH's phenanthrene derivatives—were clinically tested in human subjects, primarily neurosyphilitics, prisoner volunteers, and servicemen (16). This clinical testing, international in its scope, was overseen by James A. Shannon, trained as a physician and physiologist, whom Rolla Dyer would bring to the NIH in the years immediately following the war (17). Reporting as chairman of the Clinical Panel to the CMR Board for the Coordination of Malaria Studies in March of 1944, Shannon characterized the program's first years (18):

> The direction of the early work (1942-1943) was conditioned largely by the early loss to the United Nations of their normal sources of supply of quinine, by the lack of adequate stock-pile of quinine, and by the lack of information which would permit the intelligent use of [atebrine]. Those who were intimately concerned with the malarial problem during the first year of the war may recall the gravity of the situation.
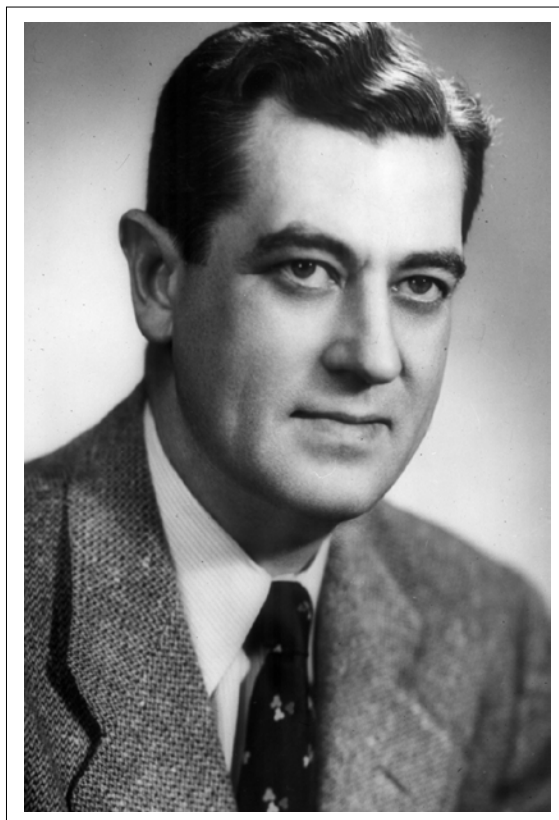
Shannon added that concern about the adequacy of atebrine compounded the worries about quinine. Shannon was an M.D.-Ph.D. at New York University working at New York's Goldwater Memorial Hospital. Early reports from the field suggested that atebrine was not adequate to the military's needs with regard to *falciparum* or *vivax* malaria. As atebrine was the drug available, the antimalarial program conducted clinical and toxicological investigations of atebrine, with the goal of optimizing its prophylactic use. Shannon, as chief of clinical research for the antimalarial program, oversaw the development of protocols for the safe and effective use of atebrine. The synthesis of new compounds and the screening of old and new ones had continued, even as work on atebrine proceeded.

In the end, Small's extensive work on phenanthrene and acridine derivatives at NIH expanded the structure-activity profiles of these promising drug series; and atebrine filled the military's needs, but all were eclipsed by the success of the 4-aminoquinolines, especially chloroquine. However, chloroquine, the wartime program's major contribution to the pharmacopoeia, was not a new compound. It had first been made and tested by Bayer in Germany during the 1930s, but the company's clinical collaborators had erroneously found the drug to be toxic. The discovery of a closely related 4-aminoquinoline, sontochin, in the possession of prisoners of war in North Africa, caused the Americans to revisit this series and rediscover chloroquine as a highly effective, low-toxicity drug for the treatment and prevention of malaria.

By August 1944, chloroquine was sufficiently promising to be extended beyond animals, and it was tested for toxicity on conscientious objectors at the Massachusetts General Hospital. No adverse toxic symptoms were observed in these preliminary trials. Further trials in malaria therapy at the Boston Psychopathic Hospital soon followed (19). The tests in Boston were just a few of many. Initial animal research expanded into testing in mental patients, prisoners, and servicemen. Testing for efficacy in humans progressed as well. Alf Alving and his group at the University of Chicago tested chloroquine and related compounds at the Stateville penitentiary. The Army expressed interest in moving ahead with "a fairly large-scale field study" of the suppressive capability of chloroquine as soon as the positive results in prisoner volunteers became available (20). The next big milestone would be tests conducted on Australian soldier-volunteers, supervised by Neil Hamilton Fairley. Fairley and his group had previously conducted advanced clinical testing on atebrine and sontochin (21). CMR

soon sent the Australian Army 2,500 chloroquine tablets with which to begin its chloroquine trial. Over time this large-scale test grew larger still: the US program arranged for 500 pounds of chloroquine to be delivered to the Australians (22). As with atebrine earlier in the war, this Australian clinical work was definitive for chloroquine progress. For the Australians, separated from the Japanese advance into South East Asia by the island of New Guinea, malaria had been a major concern and a serious problem. Fairley's unit had been called upon to determine effective protocols for quinine, atebrine, and plasmoquine. The Australians ran numerous series of tests on healthy military volunteers in Australia and New Guinea. These included heavy exercise and high altitude, to determine the effectiveness of drugs under the stress of simulated combat. Eventually, the Australian program tested not just the prewar drugs (quinine, plasmoquine, and atabrine), but sulfas, biguanides, sontochin, paludrine—the novel British antimalarial developed during the war—and chloroquine. Coatney, Shannon, and others had helped raise chloroquine from obscurity and in so doing created one of the wonder drugs of the postwar period (23).



chloroquine
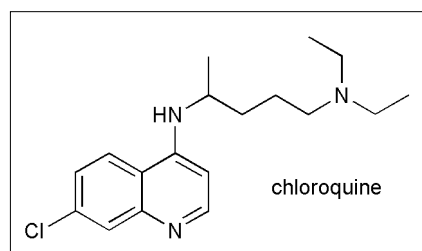
With the malaria project behind him, Shannon had a vision of what federal biomedicine, properly mobilized and funded, could accomplish. He was one substantial connection between the wartime regime and subsequent organizations, but he was not alone. Shannon, the wartime malaria researcher who oversaw the program's clinical investigations, went on to become an influential Director of NIH. He first came to work in Bethesda in 1948, at the National Heart Institute. He became Associate Director of NIH from 1952 to 1955 and Director from 1955 to 1968. Shannon, speaking about his initial NIH recruitment by Rolla Dyer (Director 1942-1950) and Norman H. Topping (Associate Director, 1948-1952), mentioned that Dyer was director of NIH by war's end, and "more importantly" that Dyer was a member CMR, which had been responsible for "the management of American Science for the military during World War II." Shannon later recalled that Dyer and Topping "knew that the wartime enterprises had been outstandingly successful, despite the complexity and breadth of the program. They felt that the

Goldwater [where Shannon had conducted his malaria work] enterprises, which were sprung up and developed in a very short period of time, [were] precisely the thing they wanted done at the new NIH—the post-war NIH." (24) Dyer, too, was well placed to appreciate Shannon's malaria work and the significance of the wider wartime program.  In his previous post he had been head of the Division of Infectious Diseases at NIH, a division that included the Malaria Office.  With malaria fading as a domestic threat to public health and the war over, the Federal health officials turned more to chronic illnesses, such as cardiovascular disease, establishing the Heart Institute at NIH in 1948 and bringing Shannon in as its associate director to oversee the new research program.  During Shannon's time at NIH its annual appropriations grew from tens of millions to more than a billion dollars (25). In the postwar decades that followed, Shannon—NIH Director from 1955-1968—and his NIH chemists would transform and expand medical research in the United States, and the growing organization would be called upon again and again to meet health emergencies.

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## ABOUT THE AUTHOR

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March 25-29, **2012**—San Diego, CA
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# ELEMENT AND RADICAL: THE DIVERGENCE OF SYNONYMS

James Togeas, University of Minnesota, Morris

The nouns "element" and "radical" are prominent words in the chemist's vocabulary.  That their meanings nowadays are radically different is a fact that is elementary to all, yet, given their prominence, it is striking that a millennium ago they were virtually synonyms. By the late eighteenth century, Lavoisier and his colleagues had assigned them different denotations.  Given the fundamental status of these two words in modern chemistry, it seems of interest to sketch the synonyms' divergent histories, which are taken in this paper through the first decades of the nineteenth century.  Inevitably, the evolution of words is about the evolution of ideas.  In this case, it is the evolving complexity of our ideas about the fundamental nature of matter that acts as a wedge to drive their meanings apart.

Empedocles (fl. 450 BCE), the Greek natural philosopher, poet, and physician of Sicily, proposed the theory of the four elements, earth, air, fire, and water, calling them the *rhizomata*, the roots of all things (1). Plato (427-347 BCE) in his dialog *Timaeus* described an atomic theory of the elements, which he called the *stoicheia*, a Greek word for the letters of the alphabet (2). Aristotle (384-332 BCE), his protégé, adopted Plato's term.  Lucretius (ca. 98-53 BCE), writing in Latin in *De Rerum Natura*, used the word *elementa* to denote both the four elements of Empedocles and the letters of the alphabet, and thus as a synonym for *stoicheia* (3).  The alchemists of the medieval West apparently thought 'roots' a better metaphor than 'alphabet,' and in Latin,

their scholarly language, "described their four elements as *radices*, corresponding to the Empedoclean *rhizomata* (4)."  Thus, earth, air, fire, and water are variously *rhizomata = stoicheia = elementa = radices*.  Element and radical are synonyms in the varied meanings above, in a qualitative way, as the roots or principles of things, but not, of course, in the quantitative sense of implying elemental composition.

When Aristotle posed the question as to the character of the elements, he wrote (5):

> An element, we take it, is a body into which other bodies may be analysed, present in them potentially or in actuality (which of these, is still disputable), and not itself divisible into bodies different in form.

A synonymous term for unanalyzable or indivisible body is "simple substance," which can then be added to the string of synonyms in the second paragraph.  Tenney L. Davis has written about the general acceptance of this definition over the centuries (6):

> Yet our abstract notion of element—the natural body or bodies, one or many, of which all things consist, from which they arise, into which they pass away—is the same today as it was in the time of LAVOISIER or BOYLE, ARISTOTLE or THALES.

There can be no objection to Davis's view on elements as far as it goes, and yet there is another facet to the definition that is the same in Aristotle and Boyle, slightly different in Lavoisier, and has disappeared entirely from our

modern thought.  For convenience this will be called the postulate of universal distribution: elements are simple substances universally distributed in nature.

For Aristotle the four undecomposable bodies are universally distributed (7):

> All the compound bodies—all of which exist in the central body—are composed of all the 'simple' bodies. ...they all contain Earth...all contain Water...and they contain Air and Fire...

The version by Robert Boyle (1627-1691) is an oft-quoted definition of element, although it is not unusual to find that the concluding phrase, the one about universal distribution, has been omitted (8):

> And now to prevent mistakes, I must advertize You, that I now mean by Elements, as those Chymists that speak plainest do by their Principles, certain Primitive and Simple, or perfectly unmingled bodies; which not being made of any other bodies, or of one another, are the Ingredients of which all those call'd perfectly mixt Bodies are immediately compounded, and into which they are ultimately resolved: now whether there be any one such body to constantly be met with in all, and each, of those that are said to be Elemented bodies, is the thing I now question.

Although Aristotle and Boyle agree on definitions, they reach different conclusions.  Boyle contends that earth, air, fire, and water are not elements because they are not universally distributed.  In fact, he doubts whether there are any elements at all and concludes that chemical theory must be framed as a theory of corpuscles.  That, however, is aside from the main path of this article; but at this point in time there seems to be no reason to think that element and radical are not synonymous.

There is a table of thirty-three simple substances in the *Elements of Chemistry* by Lavoisier (1743-1794); of those, twenty-six appear in the modern periodic table. The table is further subdivided into four categories (9). The crucial subdivision for this discussion is that elements and radicals are intersecting subsets of the set of simple substances.  In order for a simple substance to be an element, according to Lavoisier, it is (10):

> ..also necessary for it to be abundantly distributed in nature and to enter as an essential and constituent principle in the composition of a great number of bodies.

Rather than conclude like Boyle that there are no elements because there is no simple substance that obeys the strict postulate of universal distribution, Lavoisier relaxes that postulate.  In order that a simple substance be

termed an element, it is only necessary that it enter into "the composition of a great number of bodies."  There are five simple substances "belonging to all the kingdoms of nature:"  light, caloric, oxygen, azote (nitrogen), and hydrogen; and hence these are the elements.  Interestingly, charcoal (carbon) fails to make the list.

A revision of chemical nomenclature accompanied the chemical revolution of Lavoisier, with the *Méthode de nomenclature chimique* appearing in 1787, two years before Lavoisier's *Traité élémentaire de Chemie*.  Guyton de Morveau (1737-1816), who had written extensively on nomenclature, was senior author of *Méthode*.  A central idea of the new chemistry is that, in modern terminology, acids are oxides of nonmetals.  In the language of the *Méthode* oxygen is the acidifying principle, and what we term nonmetals are "acidifiable bases or radical principles (11)."  The known acidifiable bases are azote, charcoal, sulfur, and phosphorus, and the unknown the muriatic, boracic, and fluoric radicals—seven altogether. As noted above, azote appears among the elements in Lavoisier's *Traité*, and hence it is the sole point of intersection of the subset of elements and subset of radical principles of acids (12).  Evidently, the notion of radical still implies the meaning of root, since sulfur is that root that differentiates sulfuric acid in its combination with oxygen from phosphoric acid, for which phosphorus is the root or radical principle.  It is clear that the words element and radical no longer mean the same thing: some of the simple substances are elements because of their universal distribution, whereas some of those not universally distributed—nonmetals and hence principles of acids—are designated as radicals. However, although elements are simple substances, radicals may be either simple or compound.  Lavoisier summarizes the situation as follows (13):

> I have already shown, that almost all the oxydable and acidifiable radicals from the mineral kingdom are simple, and that, on the contrary, there hardly exists any radical in the vegetable, and more especially in the animal kingdom, but is composed of at least two substances, hydrogen and charcoal, and that azote and phosphorus are frequently united to these, by which we have compound radicals of two, three, and four bases or simple elements united.

The postulate of the universal or near-universal distribution of elements fades from view in the years immediately following Lavoisier's death.  During these same years the notion of a radical seems to retain a fading echo, as it were, of its former status as a simple substance.  In his researches on cyanogen, or the radical of prussic acid,

Joseph Louis Gay-Lussac (1778-1850) observed that the radical remains unaltered through a series of reactions, and that (14)

> ..when it combines with hydrogen, shows us a remarkable example, and hitherto unique, of a body which, though compound, acts the part of a simple substance in its combination with hydrogen and metals.

The same is true of the benzoyl radical, $C_7H_5O$, shown by Friedrich Wöhler (1800-1882) and Justus Liebig (1803-1873) to persist unchanged through a series of chemical transformations (15).  J. J. Berzelius, writing to the authors on the significance of their discovery, said that (16):

> ..the radical of benzoic acid is the first example proved with certainty, of a ternary body possessing the properties of an element.

Gay-Lussac had observed a binary radical that acts like a simple substance. Berzelius hailed a ternary radical with the properties of an element.  The notion proved illusory, however, that one might prepare a table of organic radicals comprising the simple substances of organic chemistry, in analogy to Lavoisier's table of simple substances.

Among ancient writers, earth, air, fire, and water were on equal footing: each was a simple substance; each was universally distributed in nature; all lay in the hidden, tangled rhizome of things; and a string of synonyms—*rhizomata* or *radices*, *stoicheia* or *elementa*—might be used for the set.  The chemistry of Lavoisier, with its list of thirty-three simple substances, was evidently more complex, and not all of the substances shared equal footing.  Lavoisier used the word element for a simple substance meeting the relaxed postulate of universal distribution.  Some simple substances were radicals, but not all radicals were simple substances; and only one element was also a radical.  Evidently, by the time of the chemical revolution and its reformation of chemical nomenclature, element and radical were no longer synonyms.

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2.    Plato, *Timaeus,* Francis M. Cornford (trans.), Bobbs-Merrill, Indianapolis, IN, 1959, § 48c.  J. R. Partington, *A History of Chemistry*, Macmillan, London, 1970, Vol. 1, 55.
3.    Lucretius, *On the Nature of Things*, W. H. D. Rouse (trans.), M. F. Smith (rev.), Loeb Classical Library, Harvard University Press, Cambridge, MA, 1975. On p 68, note "a," the translator's list all of those passages where Lucretius compares the elements to the letters of the alphabet.  Aristotle, *On Generation and Corruption*, Book II, H. H. Joachim (trans.), *Great Books of the Western World*, University of Chicago Press, Chicago, IL, Vol. 8, 1952.  Partington, Ref. 2, pp 86-90.
4.    C. G. Jung, "Alchemical Studies," R. F. C. Hull (trans.), *Collected Works*, Princeton University Press, Princeton, NJ, Vol. 13, 1967, 195.  *Radix* is the Latin singular for root.
5.    Aristotle, *On the Heavens*, Book III, § 3, J. L. Stocks (trans.), *Great Books* (Ref. 3). Since he believes that matter is continuous and not discrete, Aristotle will argue that the elements are present in bodies potentially, not actually.  Wood remains wood at every conceivable stage of subdivision; at no point could one actually encounter earth, air, fire, and water.  Hence, the elements are not present actually, but since experience shows that wood can be decomposed into them, they are present potentially.
6.    T. L. Davis, "Boyle's Conception of Element Compared with that of Lavoisier," *Isis*, **1931**, *16*, 82-91 (quote from 91).
7.    Ref. 3, § 8. The central body is either planet Earth or, more likely, the realm below the sphere of the moon.
8.    R. Boyle, *The Sceptical Chymist*, J. Cadwell, London, 1661, Kessinger Reprint, Whitefish, MT, n.d., 350 (original pagination).  For example, J. R. Partington, *A History of Chemistry,* Macmillan, London, Vol. 2, 1961, 501, omits the phrase.  Boyle also writes, "I am content to tell you that though it may seem extravagant, yet it is not absurd to doubt, whether, for ought has been prov'd, there be a necessity to admit any Elements, or Hypothetical Principles, at all," ibid., 349.
9.    A. Lavoisier, *Elements of Chemistry*, Robert Kerr (trans.), Dover reprint of the first English ed., 1790, New York, 1965, 175-6.
10.   Quoted in H. Guerlac, *Antoine-Laurent Lavoisier: Chemist and Revolutionary*, Charles Scribner's Sons, New York, 1973, 116.
11.   L. B. Guyton de Morveau, *Méthode de nomenclature chimique*, J. St. John (trans.), English ed., London, 1788; excerpted in H. M. Leicester and H. S. Klickstein, *A Source Book in Chemistry*: 1400-1900, Harvard University Press, Cambridge, MA, 1963, 184.
12.   Ref. 9, p 73. Lavoisier describes azote (nitrogen) as "the base or radical of the acid which is extracted from nitre or saltpetre."
13.   Ref. 9, p 191.  He cites one compound radical of the mineral kingdom, viz., that of aqua regia, terming it the "nitro-muriatic radical,"(p 179). It appears to this author that the last three words in the quote should be "simple substances united."

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## ABOUT THE AUTHOR

James Togeas is professor of chemistry at the University of Minnesota, Morris, where he teaches physical, general, and polymer chemistry and participates in the college's honors program.  He also teaches a one-semester course in the history of chemistry, for which he has written a text, *Atoms and Elements*.

# CALL FOR NOMINATIONS FOR THE
# 2007 EDELSTEIN AWARD

The Division of History of Chemistry (HIST) of the American Chemical Society (ACS) solicits nominations for the 2007 Sidney M. Edelstein Award for Outstanding Achievement in the History of Chemistry.  This award, first given in 2002, honors the memory of the late Sidney M. Edelstein, who established the Dexter Award in 1956, and continues the tradition of the Dexter Award for Outstanding Achievements in the History of Chemistry, which was discontinued after 2001.  Lists of previous recipients of the Edelstein Award and its predecessor Dexter Award are available at the HIST webpage (http://www.scs.uiuc.edu/~mainzv/HIST/).

The Edelstein Award is sponsored by Ruth Edelstein Barish and family and is administered by HIST.  The recipient chosen to receive the Edelstein Award is presented with an engraved plaque and the sum of $3500, usually at a symposium honoring the recipient at the Fall National Meeting of the ACS, which in 2007 will be held in Boston, MA, August 19-23.  The award is international in scope, and nominations are welcome from anywhere in the world.  Previous winners of the Dexter and Edelstein Awards include chemists and historians from the United States, Canada, Germany, France, the Netherlands, Hungary, and the United Kingdom.

A complete nomination consists of

- a complete curriculum vitae for the nominee, including biographical data, educational background, awards, honors, list of publications, and other service to the profession;

- a letter of nomination summarizing the nominee's achievements in the field of history of chemistry and citing unique contributions that merit a major award; and

- at least two seconding letters.

Copies of no more than three publications may also be included.  Only complete nominations will be considered for the award.

All nomination materials should be submitted in triplicate to William B. Jensen, Chair of the Edelstein Award Committee for 2007, Department of Chemistry, University of Cincinnati, P.O. Box 210172, Cincinnati, OH  45221-0172, USA (email: jensenwb@email.uc.edu) for arrival no later than December 31, 2006.

# BOOK REVIEWS

*Drug Discovery—A History*. Walter Sneader, John Wiley, New York, 2005, Cloth, 468 pp, $65.


I count myself fortunate to own copies of Walter Sneader's books on drug discovery: *The Evolution of Modern Medicines* (1985), *Drug Prototypes and Their Exploitation* (1996) and *Drug Discovery – A History* (2005). While it is true that each book generally addresses the topic of drug discovery with significant overlap in the material covered, it also is true that the most recent work is much more than a third edition of an existing book. As the title promises, the focus is on history. Because chemical structures are included with the text, I found the content of this book to be uniquely satisfying to a chemist interested in history. The material in this book is organized by the source of drug prototypes rather then chronological order of discovery or therapeutic indication. This aspect of the work allows one to connect the flow of information from one type of therapy to another based on medicinal chemistry knowledge and occasionally exploitation of unexpected results. To get the full value from this scheme, one must use the index to connect all of the pieces of some stories. For example, the discovery of aspirin and NSAIDs does not appear in the same section even though the drug mechanism of action and the structures are related.

Part 1 – Legacy of the Past. In this part of the book, Professor Sneader leads us through the early evolution of medical thought and practice and ties this subject to the discovery of minerals and plant substances that appeared to have therapeutic benefit. The section on mercury is particularly interesting. Study of this substance eventually led to the discovery of arsphenamine, an organomercurial used to treat syphilis and much later stimulated the discovery of the potent diuretic ethacrynic acid. This and other interesting stories set forth in this section help us to understand the evolutionary nature of drug discovery from a historical perspective.

Part 2 – Drugs from Naturally Occurring Prototypes. In this section of the book Sneader covers three important topics in the history of drug discovery. Plants, hormones, and microorganisms proved to be rich sources of new medicines after advances in science permitted isolation and purification of active components. Here we are provided with the historical background that led to initial discovery of useful activity, followed by isolation and purification of the active substance, structure determination, total synthesis, and in some cases manufacture of the drug. Morphine and quinine serve as clear examples of the complete process. Next we are informed about the discovery of hormones beginning with the era of organotherapy when people were exposed to various glandular extracts of uncertain composition in hopes of achieving some therapeutic benefit. As was the case with plant extracts, isolation and identification of physiologically active substances were key to progress toward better defined therapy. Discovery of biogenetic amines, acetylcholine, and steroids provide informative examples of how these discoveries evolved into important new drugs. This section of the book concludes with a discussion on the discovery of antibiotics produced by microorganisms.

Part 3 – Synthetic Drugs. The discovery of aspirin, hypnotics, and barbiturates provides us with interesting insight into the discovery of early drugs derived from synthesis and their contribution to the beginnings of the modern pharmaceutical industry. Set forth here also is the remarkable course of events that led from study of organic dyes to stain tissue and bacteria to discovery of anti-infective sulfonamides, carbonic anhydrase inhibitors, thiazide diuretics, alternatives to quinine for treatment and suppression of malaria, and oral hypoglycemic agents for managing diabetes. Here Sneader's organizational scheme for the book provides value to those trying to understand how one discovery can lead to another in unanticipated ways.

In the case of adrenaline, study of analogs led to agonists and antagonists. The search for a histamine antagonist was pursued by screening rather than design. This process was successful and gave us an array of therapeutically useful antihistamines. Surprisingly, this search also produced compounds that were later shown to be dopamine antagonists as well as histamine antagonists. One of these, chlorpromazine, opened the door to modern drug therapy for a variety of mental diseases. This remarkable story is one of the highlights of this book because it illustrates how closely related structures can have different biological properties. Other stories in which screening for biological activity was a critical part of an important discovery (NSAIDs, Angiotensin-II antagonists, etc.) are included in this section of the book.

I found *Drug Discovery – A History* to be an entertaining as well as an educationally enlightening read. For example, on page 360 Sneader claims that the often told story about the role of Hofmann's father in the discovery of aspirin was not as important as other events. While organization by drug prototype does require the reader to use the index carefully to put many of the stories into proper perspective, the process works. *Dr. Paul S. Anderson, 1233 Buttonwood Drive, Landsdale, PA 19446.*

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*JBC Classics and Reflections*, American Society for Biochemistry and Molecular Biology, Bethesda, MD, 2006(?), 766 pp, ISBN 1-893571-08-4, Available from: P. Roux, ASBMB, 9650 Rockville Pike, Bethesda, MD 20814-3996, $15 + $8 shipping.

This is a compendium published to celebrate the centenary of the *Journal of Biological Chemistry (JBC)*, whose first volume appeared in 1905. Each paper has already appeared in the JBC in some form. It is divided into two parts. The first part contains "Reflections" by fifty-four eminent biochemists written especially for the *JBC*. The second part ("Classics") is a set of 110 short essays by editors of the *JBC* on some important papers that appeared in the journal during its first hundred years.

Biochemists of my acquaintance know little of the history of their subject. It is good here to refer to a recent article by Jensen (1). Courses in the history of science are rare and where they exist are seldom required for any degree program. In biochemistry particularly (and especially in the molecular biology community) there is a widespread sense that the literature older than ten years is useless. This is less true in organic chemistry where a good synthesis is good forever, although perhaps not since a reading knowledge of German, in which so much of the older literature exists, is also seldom required these days. But these are arguments dealing with immediate utility. Perhaps it is more important to have one's mind stretched a bit by contemplation of how experiments were done when our current instrumentation was not available. It could be argued that a greater effort of the mind was required in those days and certainly more work.

This volume could easily be used as a textbook for a course in the History of Biochemistry. Every important area is there. It could be used in conjunction with a standard textbook in General Biochemistry as a starting point for students' essays on the history of particular areas, or it might be used in a separate course in which all of the important areas and their interrelationships are included. The volume contains many references and illustrations.

The "Reflections" are similar to the autobiographical accounts that appear in *Annual Reviews of Biochemistry* and are just as varied. Some are detailed accounts of research. These are the ones that would serve well for inquiries into the development of particular lines of research and so especially suitable for the pedagogical purposes already mentioned. Others have a broader appeal. Among these are (I cannot give page references, see below): Reichard's sad tale of why Avery never got the Nobel prize, Mildred Cohn's heroic instrumental work with du Vigneaud, Horecker's charming account of his discovery of sedoheptulose [I can supply the source of the verse that he quotes (2)], Roseman's footnotes, Westheimer on compartmentalization, the humility of H. L. Kornberg, Lehman's rejection by the JBC, Klotz's first page, Sela and serendipity, Korn and hard work, and Schachman for many reasons. Throughout, one is inspired by the joy that these people felt in their work and by the inspiration that all transmitted to their students.

There is less meat in the "Classics" section, but every one is worth reading. Note that, unlike the "Reflections," the "Classics" have not previously appeared in print; they were only available on line. This has had the reasonable consequence that supplementary material such as facsimiles of the original papers and the like are still only available on line. I also note that many of these articles cite more than one paper, so that more than 110 are discussed. Each one is coupled with some often fascinating biographical material. Many, but not all (why not?), include a picture of the eminent person.

There is so much that is excellent in this volume, but it could be improved. Perhaps these remarks will affect the second volume and even provoke a revised 2nd edition of the first. A lack of proof reading has resulted in the printing of a picture of Wyman's grandfather rather than Wyman on p 77 of "Classics." Kornberg's picture on p 239 of "Classics" also masquerades as Ochoa's on p 139. These errors have been recently corrected in an erratum sheet, but many uncorrected copies are in existence. The "Classics" section is properly paginated. However, no one took the trouble to repaginate the "Reflections." The only page numbers are the originals from the *JBC* so that, for example, Kornberg's fine article, "Remembering our Teachers," is printed as it appeared in the Jan. 5, 2001 issue with pages 3-11. This is immediately followed by Fridovich's article from August of that year with the pagination 28,629-28,636. This makes the first 492 pages difficult to navigate. In any revision, the editors should consider ordering the "Reflections" according to the birth date of the author rather than according to the date that the articles appeared in the *JBC*. Reichard's intriguing account of why Avery never received the Nobel prize sometimes names him "Osvald" and sometimes, properly, "Oswald." Where were the proofreaders? In mitigation of these criticisms, let me say that, at $23 for nearly 800 pages (on glossy paper), the collection is a tremendous bargain, but would an index—at least a name index—have increased the price so much? An index should be a priority in any future volume of the set.

It is hard to say without an index, but my impression is that Harland Wood is the most admired scientist in this collection. His picture appears many times and his praises abound. Arthur Kornberg is close behind.

I am grateful to Prof. V. Gopalan for his comments. *E. J. Behrman, Department of Biochemistry, The Ohio State University, Columbus, OH 43210.*

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*Adolf Butenandt und die Kaiser-Wilhelm-Gesellschaft: Wissenschaft, Industrie, und Politik im "Dritten Reich."* Wolfgang Schieder and Achim Trunk, Ed., Wallstein Verlag, Göttingen, 2004, 450 pp, €34.

On March 1. 1943, so Werner Heisenberg relates in his memoirs, he and Adolf Butenandt attended a lecture in the air ministry in the center of Berlin on the physiological effects of modern bombs. At the lecture's end air raid alarms sounded and the participants rushed to the shelters. They barely escaped with their lives. The two Nobel laureates made their way on foot from the center of Berlin to the distant suburbs where their homes and research centers were located. They climbed over rubble, walked around burning beams, stepped onto phosphorus which set their shoes on fire till they extinguished them in puddles. And on that walk they sketched out how Germany could make the transition from irrationality to rationality, from national defeat to peace, with Heisenberg and Butenandt guiding the process. Their emphases: the unbiased rationality of science free of politics, and a focus on Germany's youth.  Heisenberg was head of the German atom-bomb project, while Butenandt, much less well known, was a pioneer in research on sex hormones.

That episode is one of many, though few as stark, giving the reader of *Adolf Butenandt und die Kaiser-Wilhelm-Gesellschaft* an insight into life within Germany during the Nazi era.  I had worked previously on studies of two other Nobel Laureates, Fritz Haber and Heinrich Wieland, the former, of Jewish background, forced to flee Germany, while Wieland, a non-Jew, managed to keep many part-Jewish chemists in his research team. He never gave the Nazi salute.

How should one evaluate Butenandt?  He was awarded the Nobel Prize in 1939, but the Nazi regime refused to let him accept it.  This hurt.  He was never an ardent Nazi.  On the other hand he had not warmed to the Weimar Republic.  He was no democrat.  He was a patriot.  He was delighted with Hitler's successes as long as they were achieved peacefully, but his feelings changed markedly when war began and he foresaw the suffering it would entail.  By joining the party he became director of the Kaiser Wilhelm Institute of Biochemistry in Dahlem on the edge of Berlin, one of the research institutes of the national Kaiser Wilhelm Gesellschaft (hereafter KWG).  He retained this prestigious position after the war. During 1948-49 the various KWG institutes agreed to join a new organization, the Max Planck Ge-

sellschaft (MPG), Butenandt playing a not insignificant role in holding all the constituent parts together.  He was elected MPG's president in 1960 and retained the position for twelve years, after which he was named MPG's honorary president.  He died in 1995.

Hitler and the Nazis had assumed power in 1933. Two years later Butenandt visited colleagues and research centers in the U.S and was offered a professorship at Harvard, which he declined.  The Rockefeller Foundation, which almost completely terminated support of German research after 1933, continued to support Butenandt, so highly was he regarded as well as the quality of his research.

When the *Bulletin* editor asked me to review a Butenandt biography, I was reluctant.  On seeing the book, however, I quickly realized that it could be fascinating. Butenandt never admitted to any misdeeds during his many years of holding a leading position in Nazi Germany.  That raised questions and those questions are the focus of this book.  How could he, given his position and scientific stature, not be involved in Nazi-instigated biochemical studies involving humans and human materials from concentration camp inmates and victims? Accusations have been made by a number of authors though none of them, according to this book, by trained historians of science.  One major problem was the mysterious disappearance of Butenandt's locked, private secret file.  That was sufficient to cause suspicions.

The MPG cannot possibly mount investigations into the Nazi past of all its members, even all its illustrious members.  But Butenandt, as head of the Dahlem institute and later of the MPG, warranted special consideration.  A careful investigation into his role in the Nazi era would reflect for good or ill on the MPG itself.  Accordingly, the MPG gathered an international group of historians of science (U.S., British, French, German, and Austrian) to investigate every aspect of his life and work from the Nazi assumption of power in 1933 until the KWG became the MPG.

One of the two leaders of the project, Wolfgang Schieder, did cover Butenandt's life during the Weimar Republic by looking for the influences—parental, social, political, and scientific—that helped make him the man he was.  Butenandt's anti-Semitism apparently was of the conventional kind; he was never a rabid anti-Semite and valued his friendship with Otto Warburg and Otto Meyerhof.  His directorship of the biochemistry institute became possible through the forced departure of Carl Neuberg, but after the war Butenandt took steps—unsuc-

cessful as it turned out—to make possible Neuberg's return. He was, according to one author, neither a monster nor a hero of science but a rather typical example of a competent scientist in the Nazi era.  One made compromises to survive.

What about those secret archives?  They were confiscated immediately after the end of World War II by the French occupation authorities, because Butenandt had managed to move his institute from battered Berlin to the almost untouched Tübingen in the French zone. The French, we read, were less interested than the other allies in identifying war criminals, but like the others they were intensely interested in scientific and technical information they could use.  They even helped Butenandt reestablish himself in Tübingen.  Appeals to the French to release the files, or at least to allow scholars to examine them, were turned down or ignored, even when Butenandt himself appealed for them in the 1980s. Thus the eleven historians had to rely on other sources as well as interviews.  The sources included very extensive archives at the MPG as well as weekly letters Butenandt wrote to his parents from 1921 to 1959.  No evidence has surfaced incriminating Butenandt in concentration camp experiments, though he was friends with some scientists who were involved.  He even was a character witness for some and remained friends with them.

There are chapters here on German research on race differences, biochemical and otherwise, including studies looking for race-specific proteins.  We should not forget that the concern for racial purity was not an exclusively German phenomenon.  Houston Chamberlain, who wrote a seminal work on Aryan supremacy, began as an Englishman; and concerns about miscegenation are not unheard of in our country.  There is a harrowing chapter describing some of the experiments Dr. Mengele, the SS (Sturm Staffel, storm trooper) doctor and "angel of death," dreamed up and carried out at Auschwitz.

One of the problems of reviewing a collective work is how to give credit to some authors without slighting the others. Every one of these chapters is extraordinarily well and insightfully written.  And the continuity of the narrative shows the effectiveness of the scheduled discussions among the coauthors and the expert hand of the editors. But I cannot resist identifying Helga Satzinger, the author of "Adolf Butenandt, hormones and sex:  ingredients of a scientific career."

Satzinger's chapter is feminist revisionism at its best.  She focuses on the scientific contributions of Butenandt's wife, Erika Butenandt, whom he never listed as coauthor.  Yet his letters to his parents as well as other sources reveal the extent to which Butenandt, the chemist, relied on his wife's skills and knowledge in physiology. Her contribution is not mentioned in the Butenandt section of *Nobel Laureates in Chemistry* (L. K. James, Ed,) nor in studies I have seen of women centrally involved in chemical achievements.

Butenandt tended to think hierarchically: chemistry above biology, male above female, Germany above all other countries.  His institute was hierarchically organized (as was Ingold's in London when I was there) but the Dahlem Institute—unlike Ingold's—made it difficult for gifted women scientists to receive their due.  Satzinger gives details.

Just as Butenandt needed his wife to do his research, so he also needed industrial cooperation and support.  The detailed account of his cooperative work with Schering is an important study of academic-industrial cooperation involving a pharmaceutical company far smaller than the much studied giants Bayer and Hoechst.

After the war Butenandt revealed himself as an astute—nay brilliant—science manager, dedicated to science, willing to make the minimum compromises to preserve his institute and his research programs, all of which were too "pure" to leave him long on the list of suspected war criminals.  Strangely, he apparently never faced the question whether there might be ethical limits to "pure" research.  He was a consummate science-politician reestablishing and nurturing international contacts and revitalizing German science.

A final, intriguing footnote: the U.S., according to one author, did more to control every aspect of science during World War II than did Germany under the Nazis. *Otto Theodor Benfey, Greensboro, NC.*

*Chemistry, Pharmacy, and Revolution in France, 1777-1809*. Jonathan Simon, Ashgate, Aldershot, 2005; hardcover, vi + 189 pp., ISBN 0 7546 5044 8.

In this stimulating and important book, Simon explores the fate of pharmacy and its relationship with chemistry during the period indicated in his title. The period embraced two famous revolutions—the chemical revolution and the French revolution—and these events form both background and foreground for his story. His treatment explores the internal dynamics and linked trajectories of pharmacy and chemistry in France, as well as their social, political, and institutional histories.

Simon begins his story with the founding in 1777 of the Collège de pharmacie de Paris, essentially a new guild that separated French apothecaries from the épiciers (spice-merchants) with whom they had hitherto been combined. Soon thereafter the Collège was authorized to offer public courses on pharmacy, previously a right only of the Paris Faculty of Medicine. The French revolution shattered this arrangement, as it did so much else. In 1803 a new law, engineered by Antoine-François de Fourcroy, abolished the private guild structure entirely, brought pharmacy within a system of state administration and education, and created the basis for a modern pharmaceutical profession in France. From this point on, pharmacists would be trained in a series of state-run pharmaceutical schools (the Paris Collège de pharmacie, renamed Ecole de pharmacie, continuing its existence as one of these).

Already in 1797 Fourcroy, as a prominent citoyen of the French Republic, had openly placed his cards on the table. It was not enough to modernize pharmaceutical institutions in accordance with the recent revolutionary political events, he wrote. Another revolution had also taken place, the one in the science of chemistry. Chemistry, closely tied with pharmacy since its origins, had now become a true independent science, as a consequence of the transformations effected by Lavoisier's theories. Fourcroy argued that pharmacy must therefore henceforth accept a subsidiary position: pharmacists must study chemistry to become competent in their craft, not the reverse, and they must reveal all their proprietary secrets of the guild—modeling themselves after the openness of a real science. In Simon's phrase, French pharmacy "found itself suddenly subjugated to an independent discipline that seemed to appear from nowhere" (p 47). Simon concludes the chronology by discussing a brash 1809 proclamation to the Paris Society of Pharmacy by a modernist clique within the Society. These men proclaimed that "observer-pharmacists" (those properly inducted into the new science of chemistry) could no longer associate with "manipulators," mere empirical artisans. The divorce was complete, and there was no question which field dominated.

This is the outline of the story, but the book is considerably richer than that. Simon's fundamental thesis is that we cannot properly understand (and we have not hitherto properly understood) the history of French chemistry in this period without a fuller appreciation of the history of pharmacy. His argument is compelling. Most historians of eighteenth-century chemistry, Simon points out, have focused too exclusively on theory, neglecting the close connections between chemistry and its practical applications—pharmacy in the first line. Simon is, of course, not the only contemporary historian of chemistry to focus anew on the artisanal side of chymistry and early modern chemistry; one thinks of the outstanding work of Pamela Smith and Ursula Klein, for example. But for all interested in this subject, or in a refreshing new view of the chemical revolution itself, this book is highly recommended reading. *Alan Rocke, Case Western Reserve University.*

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1.   O. T. Benfey, "Dimensional Analysis of Chemical Laws and Theories," *J. Chem. Educ*., **1957**, *34*, 286-288.
2.   G. W. Wheland, *Advanced Organic Chemistry*, Wiley, New York, NY, 1949.
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6.   J. B. Conant, "Elmer Peter Kohler," *Biogr. Mem. Nat. Acad. Sci. USA,* **1952**, *27,* 264-291*.*

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