'AFFINITY': HISTORICAL DEVELOPMENT IN CHEMISTRY AND PHARMACOLOGY

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'Affinity' is a word familiar to chemists and pharmacologists. It is used to indicate the qualitative concept of 'attraction' between a drug molecule and its receptor molecule without specification of the mechanism (as in, drug A has affinity for receptor R) and to indicate a relative measure of the concept (as in, drug **A** by the following measure has greater affinity than does drug B for receptor R). It also is used to quantify the concept (as in, the affinity of drug A for receptor R is some nM value). Unfortunately, the meaning and use of affinity have diverged historically such that a pharmacologist would likely be puzzled by the recent statement in Khoruzhii *et al*. (1) "… the binding affinity, *or equivalently binding free energy* [emphasis added]…", whereas a chemist would not (2).

That different disciplines use the same term in different ways is not unusual, nor generally of much concern if the fields do not overlap. But the recent ability to measure thermodynamic parameters of drug-receptor interactions by means of isothermal titration microcalorimetry devices and other techniques (see Ref. 3), increasing use of thermodynamics in computational molecular modeling and other aspects of the study of drug-receptor interactions (see Ref. 4) and practical application to drug discovery efforts (see *e.g*., 5 and example below) portends an inevitable intersection of the different 'affinities' and likely confusion. We review the history of the use of the word affinity leading to the different contemporary definitions in chemistry and pharmacology.

Affinity as Proximity

From the derivation of the word from the Latin, it can be seen that affinity originally referred to the proximity of two things (6):

> **Affinity** [L. *affinitas*, from *affinis*, adjacent, related by marriage (as opposed to related by blood, consanguinity); *ad*, to, and *finis*, end]

This use is purely descriptive in that it refers to a situation that already exists, *i.e*., the marriage has taken place already. No predisposing or mechanistic explanation was explicit—that is, although the state of being 'related by marriage' is recognized as being attributable to emotional or social driving forces, the final state (the marriage) is not the same as what led to the marriage (the emotional and/or social driving forces). More modern use of the word denotes a *mutual attraction*, as, there is an affinity between them, or, they have affinity for each other. This is an important distinction that also underlies the divergence of definitions in the scientific use of the word. Note the subtle transition from the adjacency itself (the marriage) to the explanation of why they *remain* adjacent (*viz*., the affinity between them) and a second subtle transition towards why they *became* adjacent (*viz*., the affinity drew them together, as if it were a force).

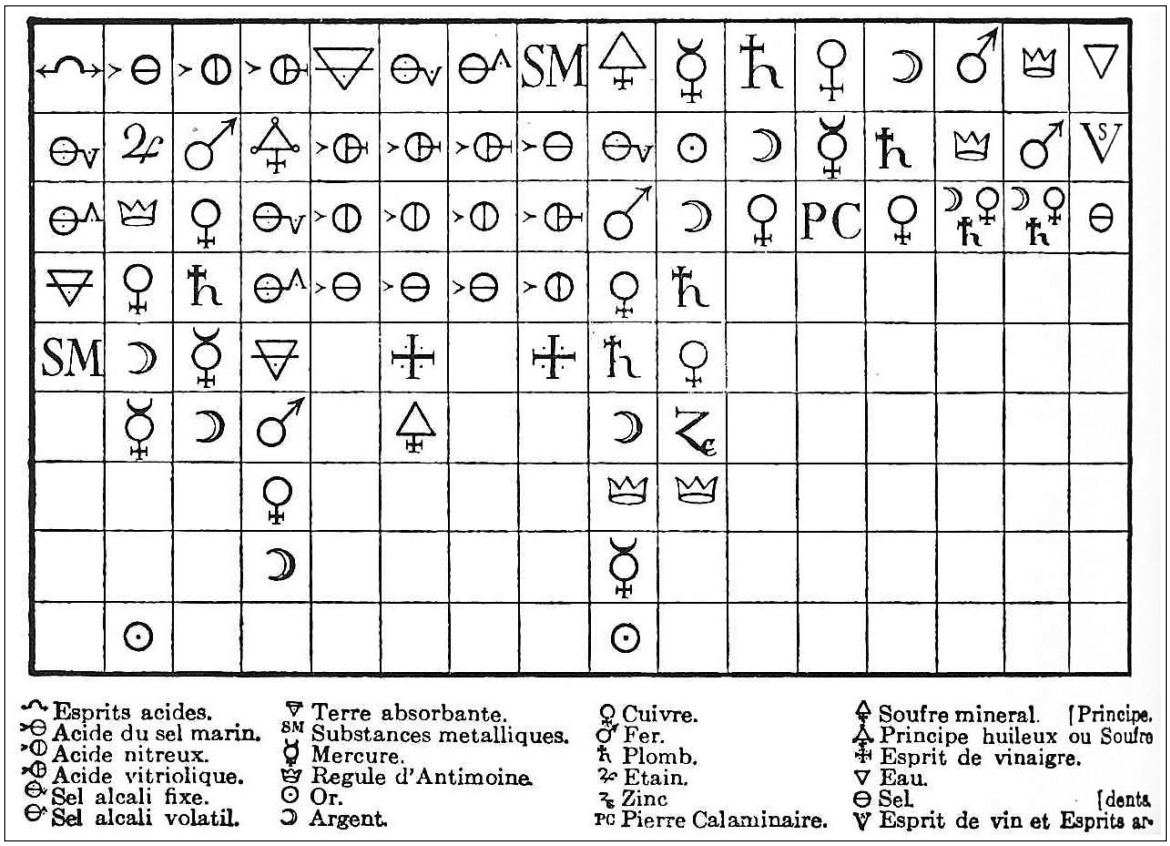

Fig 1. *The first of several affinity tables (tables des rapports) prepared by Geoffroy based on displacement reactions and presented to the French Academy (Ref. 8).*

Affinity as (Mutual) Attraction

The use of the term affinity in chemistry appears to have followed a similar transition. From the Oxford English Dictionary (7):

> *An attraction drawing to anything*
>
> 1616 [Surflet & Markh] "For this dung, by a certaine affinitie, is grateful and well liked of Bees".
>
> *Chemical attraction; the tendency which certain elementary substances or their compounds have to unite with other elements and form new compounds*
>
> 1753 [Chambers] "M. Geoffroy has given [in 1718] a table of the different degrees of affinity between most of the bodies employed in chemistry." (**Fig. 1**) (8).
>
> 1782 [Kirwan] "Chemical affinity or attraction is that power by which the invisible particles of different bodies intermix and unite with each other so intimately as to be inseparable by mere mechanical means."

In light of subsequent developments, it is instructive to see how Lavoisier (**Table 1**) used affinity in his influential 1790 book *Elements of Chemistry* (9). Noting the reversible nature of the separation and recombination of substances, he remarked (p 3):

> It is supposed, that, since the particles of bodies are thus continually impelled by heat to separate from each other, they would have no connection between themselves; and, of consequence, that there could be no solidity in nature, unless they were held together by some other power which tends to unite them, and, so to speak, to chain them together; which power, whatever be its cause, or manner of operation, we name Attraction. Thus the particles of all bodies may be considered as subjected to the action of two opposite powers, the one repulsive [which he terms caloric (10)], the other attractive, between which they remain in equilibrium.

In discussing water, Lavoisier stated that the particles of water are held together because of "reciprocal attraction" (p 4) and in the first occurrence of the word affinity in the book, used it in a remarkably modern-sounding way (p 18):

> …the proportional quantities of water imbibed by the pieces [of wood] will depend upon the nature of the

> constituent particles of the wood, and upon the greater or lesser affinity subsisting between them and water.

In a book in which such attention is given to the definitions and the derivations of the meanings of words, it is notable that affinity is used without such attention. This must indicate that most chemists of the time were familiar with and comfortable with the way Lavoisier used it. Lavoisier also makes it clear that the affinity between substances is not identical for all of them by use of terms such as "strong affinity" or "stronger affinity" (pp 74, 95, 159), inclusion of several Tables in which combinations of substances are "… arranged according to the affinities [to/with] (11) …", and explicitly in the following (p 185):

> Several conditions are requisite to enable a body to become oxygenated, or to permit oxygen to enter into combination with it. In the first place, it is necessary that the particles of the body to be oxygenated shall have less reciprocal attraction with each other than they have for the oxygen, which otherwise cannot possibly combine with them.

Interestingly, at one point (p 171), Lavoisier seems to equate, without comment, affinity and force: "… the degree of *force or affinity* [emphasis added] with which the acid adheres to the base." That this is still a new concept in 1790 is indicated by the statement on the same page that: "… even the principles upon which [this] is founded are not perhaps sufficiently accurate." However, in 1860 the connection is made explicit by Faraday (7):

> This new attraction we call chemical affinity, or the *force* [emphasis added] of chemical action between different bodies.

This date is important in relation to the work of Guldberg and Waage, of the Law of Mass Action fame, as described in the following sections.

Affinity as Driving Force

Between 1864 and 1879 affinity as used in chemistry attained a dramatically new level of quantitative and conceptual rigor in light of the advancement of the atomic theory earlier in the century by Dalton, Avogadro, and others and because of improvements in the accuracy and precision of experimental data. It might be surprising that two people who played a major role in this development were Guldberg and Waage, better known for developing the Law of Mass Action. In fact, none of the titles of their five presentations and publications in which the Law of Mass Action is developed contains the descriptor 'Law of Mass Action.' Instead, all of them contain the word affinity: "Studies concerning Affinity" (1864), "Experiments for Determining the Affinity Law" (1864), "Concerning the Laws of Chemical Affinity" (1864), "Studies in Chemical Affinity" (1867), and "Concerning Chemical Affinity" (1879).

Guldberg and Waage were schoolmates, brothers-in-law (twice), and academic colleagues (professors of applied mathematics and chemistry, respectively) at the University of Christiana (now Oslo) (for biographies, see Ref. 12). They made clear in the very first sentence of their first presentation that they were interested in studying the forces that drive chemical reactions (13):

> The theories which previously prevailed in chemistry regarding the mode of action of the chemical forces are recognized by all chemists to be unsatisfactory.

They briefly discussed the strengths and shortcomings of some previous theories of chemical affinity. For example: Bergman in 1780 (prior to modern atomic theory) proposed that each substance has its own particular affinity, but the magnitude is *independent* [emphasis added] of the mass of the substance, and Berthollet during 1801–1803 correctly proposed that the affinities of substances are dependent on their specific nature and on the original amount of the substances, but incorrectly proposed that they are also dependent on their physical character (*e.g.*, solubility or volatility).

Further historical background is given by Lund and Hassel (14). Around 1850 Williamson formulated the concept of dynamic chemical equilibrium; in 1850 Wilhelmy, called by some the father of chemical kinetics, wrote a differential equation to describe the acid-catalyzed conversion of a sucrose solution into a 1:1 mixture of glucose and fructose and found experimentally that the reaction's rate was proportional to the concentration of sucrose and acid present (15); In 1862 Berthelot and Péan de Saint-Gilles proposed a kinetic formulation for the reaction of an alcohol and an acid in which the rate is set proportional to the product of the 'active masses' (16):

> le quantité d'éther produite à chaque instant est proportionelle au produit des masses active qui sont en presence.

This is almost the Law of Mass Action, but it falls short in that it did not include the reverse reaction and it was not generalized. The work of Bergman, Berthollet, and Berthelot and Péan de Saint-Gilles was known to Guldberg and Waage, as evidenced by their reference to it in their presentation of 1864. According to Lund and Hassell (14), it appears certain that Guldberg and Waage

were not aware of the work of Wilhelmy. They clearly set out their goal (13):

> We have therefore sought to find a more direct method for determining the mode of action of these forces, and we believe that, by a quantitative investigation of the mutual interaction of different substances, we have hit upon a way which will most surely and naturally lead to the goal.

In this publication (13), they specifically considered only those chemical processes that involve 'perfect' chemical compounds (17). Of direct relevance to drug-receptor interactions are those processes defined as 'simple' (18):

> For each of two simple chemical processes, two forces assert themselves, either a composing or a decomposing, or acting and a reacting, and we view it as unavoidably necessary to regard these forces together if one is to find any quantitative expression for these forces. … we very often see in chemistry that these two opposing forces simultaneously assert themselves in one and the same chemical process.. If one modifies the conditions under which the forces operate in one way or the other, then one will either cause the opposing force to become about as strongly effective as the first—and in such a case both directions of the process will be apparent simultaneously… In order to determine the size of the chemical forces, we regard it as always necessary to study the chemical processes under such conditions that both its opposite directions are apparent simultaneously … If we maintain that for a given chemical process two opposing forces are in effect, one which strives to form new substances and one which strives to restore the original compounds from the new, it is enlightening that, when in the chemical process these forces become equally large, the system is in equilibrium. That the same equilibrium state occurs under the same conditions, whether one goes one way or the other in the process, lies in the nature of the matter.

Based on a large number of their own and others' experiments, they set forth two initially separate laws: *the law of mass action* and *the law of volume action* from which the *equilibrium condition* for the forces acting on the system is derived [italics in original]. The two laws, based on concentrations, would later be combined into one. The major concepts were numbered as follows (13):

> The Action of Mass (*Massernes Virkning*)
>
> The substitution force (19), other conditions being equal, is directly proportional to the product of the masses provided each is raised to a particular exponent. If the two substances which act on each other are designated *M* and *N*, then the substitution force for these are ['substitution force', later called 'action force'] = $\alpha(M^a N^b)$ The coefficients α, *a*, and *b* are constants which, other conditions being equal, depend only on the nature of the substances.

In this initial presentation, no claim is made that *a* and *b* are the stoichiometric coefficients of the reaction. It is stated explicitly that α, *a*, and *b* are to be determined experimentally (and did not need to be whole numbers). Guldberg and Waage were justifiably circumspect about not equating the powers to the stoichiometric coefficients because they are the same only if the reaction is an *elementary* one (20). Further, it is noteworthy that Guldberg and Waage's initial formulation related force to mass, which they called the Law of Mass Action. Their rate equation, derived in later publications (see below), was based on the assumption that rate is proportional to force.

> The action of Volume (*Volumets Virkning)*
>
> If the same masses of the interacting substances occur in different volumes, then the action of these masses is inversely proportional to the volume.
>
> The Equilibrium Equation (*Ligevægtsligningen*)
>
> 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, according to the first law 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 which keep each other in equilibrium are the action force for the first two substances is $\alpha(p-x)^a(q-x)^b$ and the reaction force for the last two is $\alpha'(p'+x)^{a'}(q'+x)^{b'}$. Since there is equilibrium, $\alpha(p-x)^a(q-x)^b = \alpha'(p'+x)^{a'}(q'+x)^b$ [where primed symbols represent the 'reverse' reaction].

This equation is credited with being the first generalized mathematical formulation of the condition of dynamic chemical equilibrium (21).

Later in the same year (1864) Guldberg and Waage took up the question of the relationship between time and a chemical reaction (*i.e.*, the reaction rate) and considered it reasonable to assume that the rate of a 'simple' chemical reaction is proportional to the driving force of the reaction. They stated (21):

> Let *p* and *q* be the number of molecules of A and B, *v* the velocity, *t* the time, and x the quantity which has transformed during this time. Then one has, regarding the total volume to be constant
>
> $$v = \frac{dx}{dt} = k(p-x)^a(q-x)^b$$

> where k is a constant depending on the nature of the bodies, the volume, the temperature, and the solvent.

There are two points worth noting about this equation. First, it is the one that is often cited as the Law of Mass Action, whereas the originators explicitly gave that name not to this equation relating reaction rate to mass, but to the equation relating driving force to mass. Thus, the equation for rate was an extension of the equation for force, not the other way around. Second, the rate equation is much less general than the force equation, subject to many more restrictions.

The clear association of affinity with force was emphasized a few years later in 1867 and finally in 1879 (22) when Guldberg and Waage presented a more elaborate and refined version of their ideas. There was a critical new feature (14, 21): The exponents in their equations were presented as integral powers of the concentration. Deviations from integer values were to be viewed as due to experimental error or to secondary forces, just the opposite of their original view about the exponents. For a reaction of the type $\alpha A + \beta B + \gamma C$, the rate is expressed as being equal to $kp^{\alpha} q^{\beta} r^{\gamma}$. This is the first time their exponents were definitely stated to be equal to the number of like molecules that take part in the reaction (23), and k was given the name affinity coefficient [underline ours].

This publication essentially marks the end of the first stage in the history of the development of affinity. In short, the meaning of affinity transitioned from an attribute (substances *have* affinity) to a force (the driving force of a chemical reaction *is* the affinity).

Of significance for subsequent use of the term in pharmacology, it should be noted that for a bimolecular drug-receptor interaction at equilibrium (in the notation of Guldberg and Waage), the forward (nonprimed) and reverse (primed) forces are equal: $kpq = k'p'q'$, so

$$\frac{k'}{k} = \frac{pq}{p'q'}.$$

The right-hand side of this equation is familiar as the 'dissociation constant' (reciprocal of the equilibrium constant). The left-hand side is the ratio of what we would today call the 'rate constants' (k and k'), but Guldberg and Waage called 'affinity coefficients.' It is easy to see—in the absence of further developments—why the dissociation constant might be erroneously thought to be the same as affinity.

Affinity as Reaction Free Energy Change

During the time Guldberg and Waage were publishing their accomplishments, others were beginning to quantify the rate of reactions in terms of the numbers, or mass, or concentration of the reactants. van 't Hoff, for example, proposed a rate law for the same data of Berthelot and Péan de Saint-Gilles used by Guldberg and Waage (**24**). More importantly, it was around this time that new ideas about heat, energy, and thermodynamics were being developed by Count Rumford (Benjamin Thompson), Carnot, Clapeyron, Mayer, Joule, Rankine, Helmholtz, Clausius, Lord Kelvin (William Thomson), Maxwell, Boltzmann, and others (25). Pfaundler von Hadermur and Horstmann were among the first to apply emerging thermodynamic principles to chemical equilibrium (21); Gibbs provided the most comprehensive treatment (26).

As a consequence of these developments, earlier concepts such as 'driving force' were considered to be too vague. Instead, chemical reactions were viewed as occurring with a change in internal energy, equal to the difference between energy content of the reactants and products. Formulated in terms of more easily measured quantities, chemical reactions proceed with a net change in enthalpy (ΔH), entropy (ΔS), or most commonly, both (29, 30). Two factors are involved in determining the occurrence and direction of a chemical reaction: the system seeks to minimize its energy and maximize its entropy. Since both usually occur during a chemical reaction (drug-receptor interaction), and often in opposition, some approach must be devised to represent the optimization process. The most convenient way was by introduction of the concept of free energy (energy available to do useful work). Chemical reactions occur in the direction in which free energy decreases (*i.e.*, the change in free energy is negative) and continues until the free energy is a minimum. In the case of a reversible reaction such as a drug-receptor interaction, the minimum is reached (and defines) the equilibrium state, a point at which the system cannot perform useful external work.

Several formulations have been proposed for representing free energy. The most useful for the type of reactions typical of drug-receptor interactions, *i.e.*, isothermal and isobaric, is the Gibbs free energy. The free energy change is usually given in the form $\Delta G = \Delta H - T\Delta S$. This leads to the simple and extremely useful rules: $\Delta G < 0$, the

reaction proceeds spontaneously (31) in the direction as written; $\Delta G = 0$, equilibrium (steady-state); $\Delta G > 0$, the reaction proceeds spontaneously in the opposite direction as written. For drug-receptor interactions, which occur as a 'closed system' (no other matter enters or leaves) and under dilute conditions, we can simplify by using concentration rather than chemical potential (partial molar free energy) and instead of activity (a measure of non-ideal behavior). Given all of the caveats, the change in Gibbs free energy for a chemical reaction (or for a drug-receptor interaction, where drug molecule A combines with receptor molecule R to form a drug-receptor complex according to: A + R $\rightleftharpoons$ AR) is

$$\Delta_r G = \Delta_r G^\circ + \Re T \ln \frac{[AR]}{[A][R]}$$

where $\Delta_r G^o$ is the change in reaction (subscript r) standard free-energy ($\Delta_r G$) (32) compared to standard state (superscript ^{o}), an arbitrary set of conditions of temperature, pressure, *etc*., that is usually defined for convenience, and $\Re$ is the universal constant = 8.314 $JK^{-1}mol^{-1}$. At equilibrium, $\Delta_r G = 0$ and [AR]/[A][R] is the familiar equilibrium constant (K_{eq}), so at equilibrium

$$\Delta_r G^\circ = -\Re T \ln K_{eq}$$

An example of the application of thermodynamics to drug design is provided by Lafont *et al.* (33). In drug discovery, once a lead compound is identified, it is often desirable to find (design, synthesize) an analog that has greater binding affinity. From a thermodynamic point of view, this means a search for interactions that have more favorable $\Delta_r G$, which in turn means favorable enthalpy and entropy contributions. Lafont *et al*. (33) found that for the system they examined (HIV-1 protease inhibitors) the enthalpy gain associated with introduction of a hydrogen-bonding functionality was offset by an entropy loss, resulting in no gain in affinity. Close analysis of the thermodynamic parameters provided guidance for a strategy for optimizing affinity in this system.

There are two very useful equations relating chemical reactions to energy. One is general ($\Delta_r G$) and the other applies to equilibrium ($\Delta_r G^o$). But what about reactions not yet at equilibrium? Isn't that what was sought by the concept of a 'driving force'? Isn't that what was meant by affinity? This question was answered by de Donder in a series of presentations and publications during the 1920s (summarized in 34). De Donder introduced a simple way to represent the degree of progress of a reaction, designated ξ. This is easy to represent by a straight line, where the origin, ξ = 0, represents the reaction before it begins (all reactants and no products) and ξ = 1 represents the reaction at its completion (all products and no reactants) (35). In drug-receptor terminology (5), ξ = 0 represents dissociated drug and receptor and ξ = 1 represents complete association as drug-receptor complex. Thus the free energy (G) is a function of ξ and can be graphed relative to ξ (progress of reaction) as displayed in **Fig 2**. For reversible reactions, the free energy is a minimum at the point where the forward and reverse reactions balance ($\Delta_r G = 0$) and is larger on either side of equilibrium, indicating that the reaction can proceed in both directions, depending on the concentrations of reactants and products. Rather than the static information, it would be preferable to have a way of indicating the change in free energy as a function of extent of reaction—in other words, the equivalent of the long-sought *driving force.*

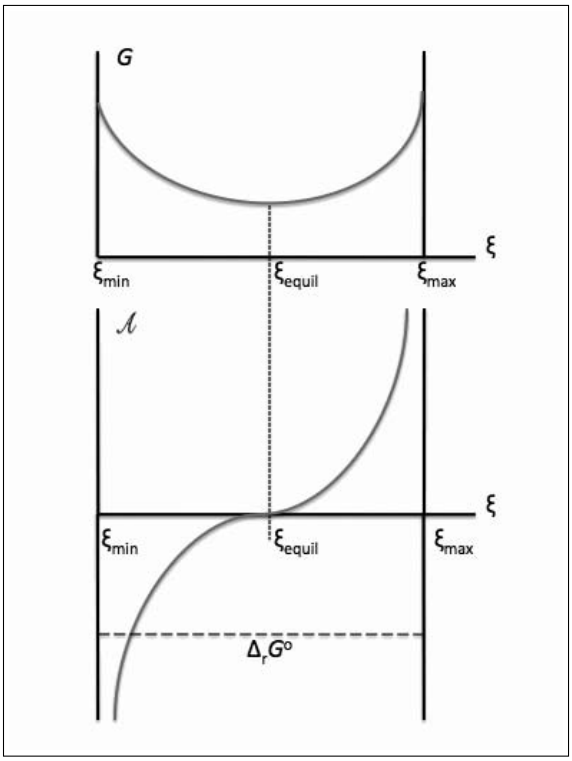

Fig 2. *The free energy (G) and affinity (***A***) graphed as functions of the extent of a chemical reaction (ξ) as the reaction proceeds—either from the left (in the direction reaction written: e.g., binding of drug with receptor to form drug-receptor complex) or from the right (opposite the direction reaction is written: e.g., dissociation from the drug-receptor complex)—towards equilibrium (at which G is minimum and* **A** *= 0).*

De Donder provided the answer when he defined affinity (**A**) such that, in the usual case of constant pressure and temperature,

$$\mathbf{A} = -\left(\frac{\partial G}{\partial \xi}\right)_{pT} = -\Delta_r G$$

This function is shown in **Fig. 2** 36, 37). Unlike *G*, the affinity indicates the direction of the reaction: when $\mathbf{A} < 0$, the drug-receptor interaction proceeds in the forward direction (association); when $\mathbf{A} > 0$, it proceeds in the reverse direction (dissociation); and $\mathbf{A} = 0$ when both are equal (equilibrium). The magnitude of affinity also represents the thermodynamic 'distance' from equilibrium. The larger the magnitude of **A** (either positive or negative), the further the interaction is from equilibrium and the interaction will proceed spontaneously toward equilibrium until $\mathbf{A} = 0$. Thus, we see the utility of affinity defined this way.

Affinity in Pharmacology

The history of the use of affinity in pharmacology is much less extensive than that of its use in chemistry. Langley, who is considered a father of receptor ('receptive substance') pharmacology, used the term affinity (38) in a manner that at first might seem qualitative, but careful reading implies that he was aware of the work of Guldberg and Waage and was using the term in the same manner (38):

> Until some definite conclusion as to the point of action … is arrived at it is not worth while to theorise much on their mode of action; but we may, I think, without much rashness, assume that there is some substance or substances … with which both [drugs] are capable of forming [drug-receptor complexes]. On this assumption then the … [complexes] are formed according to *some law of which their relative mass and chemical affinity* [emphasis added] for the substance are factors.

This was not an accidental use of terms as demonstrated two sentences later in a general example and reiteration of the terms, including specific repetition of the use of 'chemical affinity' rather than merely affinity. Chemists continue to describe affinity in such terms (39):

> …firstly, there is the *affinity* of the small molecule for the receptor binding site. Affinity is a measure of the binding free energy between the partners.

So where did the common contemporary use of affinity in pharmacology, as the reciprocal of the dissociation constant, originate? Erhlich, who coined the word 'receptor' in 1900, used the term 'specific affinity,' but not in a chemical or mechanistic way (40). Of the more quantitative early pharmacologists, Clark did not discuss affinity in his 1937 text (41), and neither did Gaddum in his extensive 1953 review (42). So one must look elsewhere for the different uses of this term by pharmacologists and chemists. There seem to be two reasons. First, the formal equivalence of affinity and the Gibbs reaction free energy change led some chemistry and thermodynamics authors to use the latter instead of the former term; second, the extensive pioneering and influential work of Ariëns and colleagues as presented in a series of articles published starting in the 1950s.

It is impossible to overestimate the importance of Ariëns in the development of drug-receptor theory and its widespread dissemination and application. He and his colleagues systematized the thinking about drug-receptor interactions and they promoted approaching the subject in a quantitative way. An example of this was the distinction between two properties of the drug-receptor interaction. One was the binding process itself and the other was the ability to induce a biological effect. This distinction helped explain competitive antagonism: an agonist possesses both properties; an antagonist possesses the first, but not the second (intrinsic activity = 0). For the first property, Ariëns used the term affinity; for the second, he used the term 'intrinsic activity.'

From the beginning, Ariëns referred to the law of mass action as the basis for his treatment of the drug-receptor interaction (43). Given his training in chemistry, it is a bit surprising that he cites Michaelis-Menten, but does not discuss the use of affinity as used by Guldberg and Waage, but writes (43):

> This means that the numbers of receptors that will be occupied at a definite concentration of A [drug] depends on the affinity between R [receptor] and A depends on the affinity between R and A thus on the reciproke [sic.] of what is mostly called the dissociation constant (K_A) of complex RA. *Affinity thus is a substance constant determining for given conditions of concentration etc. how much of the drug-receptor complex will be formed* [emphasis in original].

This view is reinforced a few pages later by "… with different *affinities* for the receptor (dissociation constants …)." This meaning of affinity is maintained throughout subsequent studies (44).

Thus we have come almost full circle. But Ariëns also writes (44):

Table Names and Dates of Prominent Scientists in the History of 'Affinity'

Name	**Birth – Death**
Everhardus Jacobus Ariëns	1918 – 2002
Torbern Olof Bergman	1735 – 1785
Pierre Eugène Marcellin Berthelot	1827 – 1907
Claude-Louis Berthollet	1748 – 1822
Ludwig Eduard Boltzmann	1844 – 1906
Nicolas Léonard Sadi Carnot	1796 – 1832
Benoît Paul Émile Clapeyron	1799 – 1864
Alfred Joseph Clark	1885 – 1941
Rudolf Julius Emanuel Clausius	1822 - 1888
Theophile Ernest de Donder	1872 – 1957
Paul Erhlich	1854 – 1915
Sir John Henry Gaddum	1900 – 1965
Étienne François Geoffroy	1672 – 1731
Josiah Willard Gibbs	1839 – 1903
Cato Maximilian Guldberg	1836 – 1902
Léopold Pfaundler von Hadermur	1839 – 1920
Hermann Ludwig Ferdinand von Helmholtz	1821 – 1894
James Prescott Joule	1818 – 1889
John Newport Langley	1852 – 1925
Antoine-Laurent Lavoisier	1743 – 1794
James Clerk Maxwell	1831 – 1879
Julius Robert von Mayer	1814 – 1878
William John Macquorn Rankine	1820 – 1872
Léon Péan de Saint-Gilles	1832 – 1863
Sir Benjamin Thompson (Count Rumford)	1753 – 1814
William Thomson (Lord Kelvin)	1824 – 1907
Jacobus Henricus van 't Hoff	1852 – 1911
Peter W. Waage	1833 – 1900
Ludwig Ferdinand Wilhelmy	1812 – 1864
Alexander William Williamson	1824 – 1904

> It is worth while to realize that what is defined here as affinity [emphasis in original] is what is generally called the activity of a drug: a drug is "active" if it shows an effect in low concentration i.e. when it has high affinity.

The circle is now completed. Affinity has been restored to its qualitative vernacular use, and it also has a precise definition: reciprocal of the dissociation constant. But the definition seems to have been formulated in a way that was independent of the developments of affinity in chemistry. It is not clear why a new term was created for the reciprocal of the dissociation constant (K_d), since $1/K_d$ already had a well-known name—the equilibrium constant. Furthermore, by defining affinity in terms of an equilibrium constant, its meaning reverts to a completed event (proximity, marriage) rather than to the driving force. Nevertheless, this use has persisted in pharmacology.

Summary and Perspective

Colloquial use of the term affinity evolved historically from meaning 'proximity' to meaning 'attraction.' Scientific use of affinity underwent a similar evolution and as traced in this review further evolved in chemistry and thermodynamics to quantify the driving force of chemical reactions. Pharmacology developed a related, but different definition for affinity. The different fields could continue to define and use affinity in different ways, but confusion might arise as thermodynamics is increasingly used in practical applications in drug-discovery (5, 45). Recognition of the differences and some type of unification would seem worthwhile.

REFERENCES AND NOTES

1. O. K. Khoruzhii, A. G. Donchev, N. Galkin, A. Illarionov, M. Olevanov, V. Ozrin, C. Queen, and V. Tarasov, "Application of a Polarizable Force Field to Calculations of Relative Protein–ligand Binding Affinities," *Proc. Natl. Acad. Sci. USA*, **2008**, *105*, 10378–10383.
2. D. Colquhoun, "The Quantitative Analysis of Drug-receptor Interactions: A Short History," *Trends Pharmacol. Sci*., **2006**, *27*, 149–157.
3. S. Leavitt and E. Freire, "Direct Measurement of Protein Binding Energetics by Isothermal Titration Calorimetry," *Curr. Opin. Struct. Biol*., **2001**, *11*, 560–566; R. B. Raffa, "Experimental Approaches to Determine the Thermodynamics of Protein-ligand Interactions," in H-J. Böhm and G. Schneider, Ed., *Protein-Ligand Interactions: From Molecular Recognition to Drug Design*, Wiley-VCH, Weinheim, 2003, 51–71; A. Velazquez-Campoy and E. Freire, "Isothermal Titration Calorimetry to Determine Association Constants for High-affinity Ligands," *Nature Protocols*, **2006**, *1*, 186–191 (2006).
4. E. Freire, "Statistical Thermodynamic Linkage between Conformational and Binding Equilibria," *Adv. Protein Chem*., **1998**, *51*, 255–279; R. B. Raffa "(Extra)thermodynamics of the Drug-receptor Interaction," *Life Sci*., **1999**, *65*, 967–980; J. A. D'Aquino, E. Freire, and L. M. Amzel "Binding of Small Organic Molecules to Macromolecular Targets: Evaluation of Conformational Entropy Changes," *Proteins (Suppl)*, **2000**, *4*, 93–107.
5. R. B. Raffa, Ed., *Drug–Receptor Thermodynamics: Introduction and Applications*, John Wiley & Sons, Chichester, 2001.
6. http://www.merriam-webster.com/dictionary/affinity (accessed February 21, 2009).
7. http://www.oed.com (accessed February 21, 2009).
8. http://en.wikipedia.org/wiki/Chemical_affinity (accessed February 21, 2009).
9. A-L. Lavoisier, *Elements of Chemistry,* 1790; (translation by R. Kerr, Dover Publications, New York, 1965, 1–511).
10. 'Caloric' was carefully differentiated from heat, and (p 5): "… strictly speaking, we are not obliged to suppose this to be a real substance; it being sufficient … that it be considered as the repulsive cause, whatever that may be, which separates the particles of matter from each other."
11. The assignment of relative affinity was cleverly based, for example, on relative ability to form precipitates (p 127): "If … any sulphuric acid is suspected in the nitric acid, it is easily separated by dropping in a little nitrate of barites, so long as any precipitation takes place; the sulphuric acid, from its greater affinity, attracts the barites, and forms with it an insoluble neutral salt, which falls to the bottom."
12. H. Haraldsen, "Cato Maximilian Guldberg (1836–1902) and Peter Waage (1833-1900)" in O. Bastiansen, Ed., *The Law of Mass Action: a Centenary Volume*, Universitetsforlaget, Oslo, 1964, 19–35.
13. P. Waage and C. M. Guldberg, "Studies concerning Affinity," *Forhandlinger Videnskabs-Selskabet i Christiania* [Proceedings of the Norwegian Academy of Science and Letters], Oslo, **1864**, 35-45; a facsimile of the Norwegian original (minus some figures) is available in O. Bastiansen, Ed., *The Law of Mass Action: a Centenary Volume*, Det Norske Videnskaps-Akademi Universitetsforlaget, Oslo, 1964, 7–17; an English translation of the facsimile is available by H. I. Abrash "Studies Concerning Affinity (P Waage and CM Guldberg)," *J. Chem. Educ*., **1986**, *12*, 1044–1047.
14. E. W. Lund and O. Hassel, "Guldberg and Waage and the Law of Mass Action," in O. Bastiansen, Ed., *The Law of Mass Action: a Centenary Volume*, Universitetsforlaget, Oslo, 1964, 37–46.
15. L. Wilhelmy, "Ueber das Gesetz, nach welchem die Einwirkung der Säuren auf den Rohrzucker stattfindet," [The law by which the action of acids on cane sugar occurs] *Pogg. Ann. Phys. Chem*., **1850**, *81*, 413–433. Excerpts are available at http://web.lemoyne.edu/~giunta/wilhelmy.html (accessed February 21, 2009).
16. M. Berthelot and L. Péan de Saint-Gilles, "Essai d'une théorie sur la formation des Éthers. *Ann. Chim. Phys*., **1862**, *66*, 110–128.
17. "… any phenomenon in which the chemical forces bring about a chemical change in the material; … always occur according to particular atomic relationships."
18. "… direct combination of two molecules to a new molecule [in drug-receptor interactions, the drug-receptor complex] (addition) and, in reverse, splitting of the molecule into two others [dissociation]."
19. This statement was restricted to "simple" processes in which "a mutual exchange or substitution of the constituent parts of two molecules and, in reverse, regeneration of the original molecule by a backwards substitution. One could call the one action and the other reaction.
20. An elementary reaction is one that occurs exactly as written in a single step, with no intermediate steps, *i.e*., the reaction as written represents the actual physical combination of atoms and does not represent a net reaction consisting of several steps.
21. E. W. Lund, "Guldberg and Waage and the Law of Mass Action," *J. Chem. Educ*., **1965**, *42*, 548–550.
22. It is said that the final publication was stimulated by the impression that their previous work had not been sufficiently known, possibly because it was in periodicals not readily available to chemists outside Norway (Ref. 14, 15).
23. According to Lund (Ref. 14) the first appearance of the exponents as being equal to the coefficients in the chemical equation is due ("as far as it has been possible to determine") to A. F. Horstmann (1842–1929) in a paper published in 1877.

24. J. H. van 't Hoff, "Die Grenzebene ein Beitrag zur Kenntniss Esterbildung," *Ber. Dtsch. Chem. Ges.*, **1877**, *10*, 669–678.
25. M. Guillen, *Five Equations that Changed the World*, Hyperion, New York, 1995.
26. For a convenient timeline of the development of thermodynamics, see Ref. *27;* and for a clear and readable explanation of thermodynamics concepts applied to pharmaceutical systems, see Connors (Ref. 28).
27. http://en.wikipedia.org/wiki/Timeline_of_thermodynamics,_statistical_mechanics ,_and_random_processes (accessed February 21, 2009).
28. K. A. Connors, *Thermodynamics of Pharmaceutical Systems*, John Wiley & Sons, Hoboken, NJ, 2002.
29. G. N. Lewis and M. Randall, *Thermodynamics*, McGraw-Hill Book Co, New York, 2nd ed. revised by K. S. Pitzer and L. Brewer, 1961, 1–723.
30. E. B. Smith, *Basic Chemical Thermodynamics,* Clarendon Press, Oxford, 4th ed, 1995, 1–166,
31. The *rate* of the spontaneous reaction is not predictable by $\Delta_r G$.
32. Some authors use a prime or other symbol to indicate that this applies to precisely defined conditions.
33. V. Lafont, A. A. Armstrong, H. Ohtaka, Y. Kiso, L. M. Amzel, and E. Freire, "Compensating Enthalpic and Entropic Changes Hinder Binding Affinity Optimization," *Chem. Biol. Drug Design*, **2007**, *69*, 413–422.
34. T. De Donder and P. Van Rysselberghe, *Thermodynamic Theory of Affinity*, Stanford University Press, Stanford, CA, 1936, 1–142.
35. More precisely, but not necessary for the present discussion, $\xi_{min} < \xi < \xi_{max}$.
36. M. Graetzel and P. Infelta, *The Bases of Chemical Thermodynamics,* Universal Publishers, Parkland FL, 2000, Vol. 1, 2.
37. P. Perrot, *A to Z of Thermodynamics*, Oxford University Press, Oxford, 1998.
38. J. N. Langley, "On the Physiology of the Salivary Secretion," *J. Physiol.*, **1878**, *1*, 339–369.
39. W. G. Richards, *Quantum Pharmacology*, Butterworths, London, 1977, 20; J. K. Baird, "A Generalized Statement of the Law of Mass Action," *J. Chem. Educ.*, **1999**, *76*, 1146–1150.
40. J. Parascandola and R. Jasensky, "Origins of the Receptor Theory of Drug Action," *Bull. Hist. Med.*, **1974**, *48*, 199–220; C-R. Prüll, "Part of a Scientific Master Plan? Paul Ehrlich and the Origins of his Receptor Concept," *Med. Hist.*, **2003**, *47*, 332–356; F. Bosch and L. Rosich, "The Contributions of Paul Ehrlich to Pharmacology: a Tribute on the Ocasion of the Centenary of his Nobel Prize," *Pharmacol.*, **2008**, *82*, 171–179.
41. A. J. Clark, "General Pharmacology" in B. Von A. Hefter, Ed., *Handbuch der Experimentellen Pharmakologie,* Julius Springer, Berlin, 1937, Vol. 4. .
42. J. H. Gaddum, "Bioassays and Mathematics," *Pharmacol. Rev.*, **1953**, *5*, 87–134.
43. E. J. Ariëns, "Affinity and Intrinsic Activity in the Theory of Competitive Inhibition," *Arch. Int. Pharmacodyn.*, **1954**, *49*, 32–49.
44. E. J. Ariëns, A. J. Beld, J. F. Rodrigues de Miranda, and A. M. Simonis, "The Pharmacon–receptor–effector Concept," in R. D. O'Brien, Ed., *The Receptors: a Comprehensive Treatise*, Plenum, New York, 1979, 33–91.
45. P. Gilli, G. Gilli, P. A. Borea, K. Varani, A. Scatturin, and A. Dalpiaz, "Binding Thermodynamics as a Tool to Investigate the Mechanisms of Drug-receptor Interactions: Thermodynamics of Cytoplasmic Steroid/nuclear Receptors in Comparison with Membrane Receptors," *J. Med. Chem.*, **2005**, *48*, 2026–2035; G. A. Holdgate and W. H. Ward, "Measurements of Binding Thermodynamics in Drug Discovery," *Drug Discov. Today*, **2005**, *10*, 1543–1550.
46. B. H. Mahan, *Elementary Chemical Thermodynamics*, W.A. Benjamin, New York, 1964.

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